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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

OTSUKA PHARMACEUTICAL CO., LTD., Plaintiff, v. SANDOZ, INC., TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., BARR LABORATORIES, INC., BARR PHARMACEUTICALS, INC., APOTEX CORP., APOTEX INC., SUN PHARMACEUTICAL INDUSTRIES, LTD., SYNTHON HOLDING BV, SYNTHON BV, SYNTHON PHARMACEUTICALS, INC., and SYNTHON LABORATORIES, INC., Defendants.	**Consolidated Civil Action No. 3:07-cv-01000 (MLC)(LHG)** Honorable Judge Mary L. Cooper **Magistrate Lois H. Goodman** Document Electronically Filed **PLAINTIFF'S POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW**

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

FEDERAL CASES

FEDERAL STATUTES

REGULATIONS

I. INTRODUCTION

Trial established that aripiprazole is a pioneering invention in the field of antipsychotic drug discovery. No other antipsychotic resembles aripiprazole either chemically or pharmacologically. The undisputed evidence shows that aripiprazole is: (1) the only antipsychotic drug that is a "carbostyril derivative"; (2) the only antipsychotic drug with a "butoxy linker"; (3) the only antipsychotic drug with a "2,3-dichloro" substituted phenyl ring; (4) the only antipsychotic drug that is a "partial agonist" at dopamine receptors or that exhibits "functional selectivity"; and (5) the only antipsychotic drug with its unique combination of interactions at serotonin, dopamine, and other receptors in the brain as shown by Dr. Roth's "heat map." Moreover, aripiprazole's novel chemistry and pharmacology yield something even more important: a therapeutically effective atypical antipsychotic drug that treats the debilitating positive symptoms of schizophrenia while maintaining a highly favorable side-effect profile.

Defendants, seeking to copy aripiprazole, now assert that "routine optimization" of prior art compounds somehow would have led to aripiprazole. This argument is absurd. Dr. Oshiro did not "optimize" OPC-4392 or the unsubstituted butoxy compound. After learning of OPC-4392's failure in clinical trials, he decided that Otsuka needed to go back to the drawing board and find a compound that, *unlike* OPC-4392, potently inhibited apomorphine-induced stereotypy in mice. His insight, persistence, and scientific skills ultimately led to his discovery of aripiprazole. There was nothing "routine" about his invention. Tellingly, although scientists have been trying to replicate aripiprazole's unique properties since at least 1994 (when aripiprazole's successful clinical results were published), no other antipsychotic drug like aripiprazole has been discovered to date.

The hypothetical person of ordinary skill in the art in October 1988 never would have discovered aripiprazole. Antipsychotic drug research in the 1980s was highly unpredictable, replete with failures, and driven by several competing, largely unproven hypotheses of atypical antipsychotic drug action—none of which would have led to aripiprazole. The person of ordinary skill would have *avoided* carbostyril derivatives as potential antipsychotics because the only such compound to even make it to clinical trials, OPC-4392, failed to treat the positive symptoms of schizophrenia. Instead, the person of ordinary skill would have made analogs of known antipsychotics such as clozapine or risperidone. Indeed, Defendants' only expert witness with any experience in antipsychotic drug discovery, Dr. Press, worked *exclusively* on clozapine-like potential antipsychotics and never made any carbostyril derivatives. Consistent with Otsuka's position, all currently marketed atypical antipsychotics except aripiprazole are based on clozapine or risperidone.

The absence of any evidence that a person of ordinary skill would have selected a carbostyril derivative such as OPC-4392 or the unsubstituted butoxy compound as a "lead compound" over other prior art compounds is fatal to Defendants' obviousness defense. *See, e.g.*, *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 2010 U.S. App. LEXIS 18820, at *18 (Fed. Cir. Sept. 9, 2010) (holding that, post-*KSR*, obviousness of a chemical compound "still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had reason to select a proposed lead compound or compounds over other compounds in the prior art"). Defendants fail to cite *Daiichi* even though this recent precedential decision from the Federal Circuit is directly on point and dispositive of their arguments.

Apparently recognizing the weakness of their obviousness defense, Defendants advance essentially the same obviousness arguments under an alternative theory of obviousness-type double

patenting. As a matter of law, however, because the '416 patent is prior art to the '528 patent, there is no separate obviousness-type double patenting issue. The obviousness and obviousness-type double patenting issues collapse into the same legal analysis. *See, e.g., Sanofi-Synthelabo v. Apotex Inc.*, 492 F. Supp. 2d 353, 393 (S.D.N.Y. 2007), *aff'd*, 550 F.3d 1075 (Fed. Cir. 2008). In any event, the evidence shows that aripiprazole is patentably distinct from the unsubstituted butoxy compound. Defendants' obviousness-type double patenting defense therefore cannot succeed.

Most fundamentally, the Court should reject Defendants' invalidity and inequitable conduct defenses because they are unsupported by the evidence introduced at trial. At every turn, Defendants misconstrue the evidence. They characterize OPC-4392 as "a promising antischizophrenic drug" when it clearly failed, strain to interpret the Wise poster as teaching D_2 antagonism when it only discusses autoreceptor agonists, disregard the prior art's many teachings away from aripiprazole such as the '416 patent's description of the unsubstituted butoxy compound as an antihistamine, and engage in a tortured analysis of the Nakagawa declaration in an attempt to extract "structure-activity relationship" information from it while ignoring the actual purpose of the declaration to compare the tested compounds to the prior art. Defendants also repeatedly cite to non-prior art documents as if they were prior art.

In addition, Defendants improperly raise new invalidity and unenforceability defenses not identified in the pretrial order. *See, e.g.*, Defendants' Post-Trial Proposed Findings of Fact and Conclusions of Law dated Sept. 27, 2010 ("Def. FOFCOL"), at 99-105 (section entitled "Obviousness Based on the 2,3-Dichloro Propoxy Compound"); 149-151 (section entitled "Otsuka's Withheld Contradictory Internal Data"). In the accompanying motion, Otsuka respectfully requests that the Court strike these untimely raised new defenses. Otsuka's proposed counter-

findings/conclusions further establish that these new defenses are factually and legally baseless. Accordingly, because the '528 patent is valid, enforceable, and infringed for the reasons detailed below, Otsuka is entitled to entry of final judgment in its favor.

II. PROCEDURAL HISTORY

A. Jurisdiction

This is a civil action for infringement of U.S. Patent No. 5,006,528 ("the '528 patent"), arising under the United States patent laws, Title 35, United States Code, § *et seq.*, including 35 U.S.C. §§ 271 and 281. This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

For purposes of this civil action only, no party contests venue or personal jurisdiction.

B. Plaintiff Otsuka and Its Commercially Successful Abilify® Product

Plaintiff Otsuka Pharmaceutical Co., Ltd. ("Otsuka") is a corporation organized and existing under the laws of Japan with its corporate headquarters at 2-9 Kanda Tsukasa-machi, Chiyoda-ku, Tokyo, 101-8535, Japan. [Uncontested Fact, Pretrial Stip. at ¶ 1] Otsuka is the holder of the '528 patent, which covers, among other things, the chemical compound aripiprazole, pharmaceutical compositions containing aripiprazole, and methods of using aripiprazole to treat schizophrenia.

Otsuka is the holder of New Drug Application ("NDA") No. 21-436 for aripiprazole tablets, which the United States Food and Drug Administration ("FDA") approved on November 15, 2002. Otsuka currently lists the '528 patent in Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") for NDA No. 21-436. [Uncontested Fact, Pretrial Stip. at ¶ 28]

Otsuka markets its aripiprazole formulations that are the subject of NDA No. 21-436 under the trade name Abilify®. [Uncontested Fact, Pretrial Stip. at ¶ 29] Abilify® is a very successful drug

product, generating over $3 billion in U.S. sales in 2009 alone, making it the sixth largest selling drug in the United States. [Tr. 2020-2, 2031-4 (Jarosz)]

C. Participating Defendants

The following Defendants participated in the bench trial held from August 4 through August 26, 2010:

Defendant Teva Pharmaceuticals USA, Inc. ("Teva") is a Delaware corporation with a principal place of business in North Wales, Pennsylvania. [Uncontested Fact, Pretrial Stip. at ¶ 2]

Defendant Barr Laboratories, Inc. ("Barr Labs.") is a Delaware corporation having a principal place of business in Woodcliff Lake, New Jersey. Barr Labs. is a wholly owned direct subsidiary of Barr Pharmaceuticals, LLC. [Uncontested Fact, Pretrial Stip. at ¶ 3]

Defendant Barr Pharmaceuticals, Inc. was acquired by Teva USA on December 23, 2009, and changed its name to Barr Pharmaceuticals, LLC. Barr Pharmaceuticals, LLC is a Delaware limited liability company with a principal place of business in North Wales, Pennsylvania and is a wholly owned subsidiary of Teva USA. Defendants Barr Labs. and Barr Pharmaceuticals, LLC are collectively referred to herein as "Barr." [Uncontested Fact, Pretrial Stip. at ¶ 4]

Defendant Apotex Corp. is a Delaware corporation with a principal place of business in Weston, Florida. Defendant Apotex Inc. is a Canadian corporation with a principal place of business in Toronto, Canada. Defendants Apotex Corp. and Apotex Inc. are collectively referred to herein as "Apotex." [Uncontested Fact, Pretrial Stip. at ¶ 5]

D. Stayed Defendants

The following Defendants did not participate in the bench trial in these consolidated actions, having entered into stipulations whereby they would no longer actively participate in the

consolidated actions, but would be bound by the outcome in these actions, as specified in their individual stay agreements:

Defendant Sandoz, Inc. ("Sandoz") has stipulated to a stay of this consolidated action, Civil Action No. 07-cv-01000, according to the terms set forth in Docket Index ("D.I.") 310. [Uncontested Fact, Pretrial Stip. at ¶ 6]

Defendant Sun Pharmaceutical Industries, Ltd. ("Sun") has stipulated to a stay of Civil Action No. 07-cv-01516, now consolidated under this action, according to the terms set forth in D.I. 285 in this consolidated action. [Uncontested Fact, Pretrial Stip. at ¶ 7]

Defendants Synthon Holding BV, Synthon BV, Synthon Pharmaceuticals, Inc., and Synthon Laboratories, Inc. (collectively "Synthon") have stipulated to a stay of Civil Action No. 07-cv-04112, now consolidated under this action, according to the terms set forth in D.I. 92 in this consolidated action. [Uncontested Fact, Pretrial Stip. at ¶ 8]

As set forth in the Orders entered at D.I. 310, D.I. 285 and D.I. 92, respectively, in this consolidated action, Defendants Sandoz, Sun and Synthon have agreed to be bound by the final judgment in this case regarding the validity and enforceability of the '528 patent. [Uncontested Fact, Pretrial Stip. at ¶ 9]

Zydus Pharmaceuticals USA, Inc. and Cadila Healthcare Ltd. (collectively "Zydus") are parties to actions in this District, Civil Action Nos. 08-cv-02675(MLC) ("Zydus Action I") and 10-cv-02857 ("Zydus Action II"), not consolidated with the present action. In Zydus Action I, the parties have agreed to be bound by the final judgment in this case regarding the validity and enforceability of the '528 patent according to the stipulated order entered at D.I. 10 in Zydus Action I. [Uncontested Fact, Pretrial Stip. at ¶ 10]

E. Dismissed Defendant

Defendant Teva Pharmaceutical Industries, Ltd. ("Teva Industries") is a corporation organized under the laws of Israel with its principal place of business located at 5 Basel Street, P.O. Box 3190, Petach Tikva 49131, Israel. Teva USA is a wholly owned indirect subsidiary of Teva Industries. Teva Industries has been dismissed as a party to this action but has stipulated to be bound by any judgment, order or decision in Civil Action No. 07-cv-1000 that one or more claims of the '528 patent are not invalid and/or not unenforceable, and/or are infringed by the generic aripiprazole products Teva USA seeks FDA approval for pursuant to ANDA Nos. 78-607, 78-608 and 78-708. *See* D.I. 15 in 07-cv-01110, now consolidated with this action, and D.I. 70 in this consolidated action. [Uncontested Fact, Pretrial Stip. at ¶ 11]

F. The Defendants' ANDAs

Teva, Barr, Apotex, Sandoz, Sun, Synthon and Zydus each filed one or more Abbreviated New Drug Applications ("ANDAs") under the Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585 (known as the Hatch-Waxman Act) seeking approval from the FDA to market generic copies of Otsuka's Abilify® products. The details of the participating parties' ANDAs are as follows.

Teva USA filed ANDA Nos. 78-607, 78-608, and 78-708 under Section 505(j) of the Federal Food, Drugs and Cosmetic Act, 21 U.S.C. § 355(j) ("the Act") seeking FDA approval to market generic tablet products containing 2 and 5 mg (No. 78-607); 10 mg (No. 78-608); and 15, 20 and 30 mg (No. 78-708) of aripiprazole. [Uncontested Fact, Pretrial Stip. at ¶ 31]

Apotex Corp. filed ANDA No. 78-583 under Section 505(j) of the Act seeking FDA approval to market generic tablet products containing 5, 10, 15, 20 and 30 mg of aripiprazole. Apotex Corp.

amended its ANDA No. 78-583 seeking FDA approval to market generic tablet products containing 2 mg of aripiprazole in addition to Apotex Corp.'s 5, 10, 15, 20 and 30 mg generic tablet products. [Uncontested Fact, Pretrial Stip. at ¶ 32]

Barr Labs. filed ANDA Nos. 78-612 and 78-613 under Section 505(j) of the Act seeking FDA approval to market generic tablet products containing 2, 5, 10, 15, 20 and 30 mg of aripiprazole. [Uncontested Fact, Pretrial Stip. at ¶ 33]

Defendants filed with each ANDA identified above a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), commonly referred to as a "Paragraph IV certification," with respect to the '528 patent. [Uncontested Fact, Pretrial Stip. at ¶ 30]

G. Otsuka's Infringement Claims and Defendants' Stipulation of Infringement

Otsuka filed suit against each of the Defendants, alleging infringement of the '528 patent under 35 U.S.C. § 271(e)(2)(A). The Court consolidated the suits against Teva, Barr, Apotex, Sandoz, Sun, and Synthon into this single action. The lawsuits against Zydus have not been consolidated. The lawsuits against the participating defendants were consolidated on June 27, 2007, with the exception of Otsuka's action (Civil Action No. 08-cv-04958-MLC) against Apotex's amended ANDA No. 78-583, which was consolidated with this action on December 11, 2008. [Uncontested Fact, Pretrial Stip. at ¶ 34]

In the bench trial involving the participating defendants, Teva, Barr and Apotex, Otsuka asserted infringement of three claims of its '528 patent, claims 12, 17 and 23. [Uncontested Fact, Pretrial Stip. at ¶ 19]

Claim 12 of the '528 patent is directed to the compound aripiprazole, which has the chemical name 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril. [Uncontested Fact, Pretrial Stip. at ¶ 20]

Claim 17 of the '528 patent is directed to a pharmaceutical composition for treating schizophrenia containing, as the active ingredient, aripiprazole or a pharmaceutically acceptable salt thereof. [Uncontested Fact, Pretrial Stip. at ¶ 21]

Claim 23 of the '528 patent is directed to a method of treating schizophrenia comprising administering a pharmaceutical composition containing, as an active ingredient, aripiprazole or a salt thereof. [Uncontested Fact, Pretrial Stip. at ¶ 22]

Teva, Apotex, and Barr have each stipulated to infringement of claims 12, 17 and 23 of the '528 patent. Specifically, each of these Defendants has stipulated that the generic aripiprazole products that are the subject of their respective ANDAs, "if commercially made, used, offered for sale or sold within the United States, or commercially imported into the United States, would fall within the scope of Claims 12, 17 and 23 of U.S. Patent No. 5,006,528 to the extent those claims are valid and enforceable." *See* D.I. 224, D.I. 226 and D.I. 233 in this consolidated action. [Uncontested Fact, Pretrial Stip. at ¶ 35]

Defendants Sun and Sandoz, stayed parties to this consolidated action, have also agreed to the same stipulation. *See* D.I. 223 and D.I. 225 in this consolidated action. [Uncontested Fact, Pretrial Stip. at ¶ 36]

H. Overview of Defendants' Defenses Asserted and Conduct of Bench Trial

Because each of the participating defendants stipulated to infringement of the three claims asserted by Otsuka in this action, claims 12, 17 and 23, the only issues for trial were Defendants'

invalidity and unenforceability affirmative defenses and related counterclaims. Defendants asserted that claims 12, 17, and 23 of the '528 patent were invalid based on non-statutory obviousness-type double patenting, invalid for obviousness under 35 U.S.C. § 103, and unenforceable due to inequitable conduct. Defendants also asserted, but did not attempt to prove, a contingent invalidity argument under 35 U.S.C. § 112.

The Court held a bench trial from August 4 through August 26, 2010. Defendants proceeded first at trial presenting testimony from five expert witnesses: medicinal chemist Jeffery Press, Ph.D., behavioral neurobiologist John Marshall, Ph.D., patent attorney and former PTO examiner John T. Goolkasian, medicinal chemist Neal Castagnoli, Ph.D., and behavioral pharmacologist Richard Beninger, Ph.D.

Otsuka then presented its case through the testimony of four expert witnesses: psychopharmacologist Bryan Roth, Ph.D., M.D., statistician Ronald Thisted, Ph.D., medicinal chemist David Nichols, Ph.D., and economist John Jarosz; and two fact witnesses: lead inventor Dr. Yasuo Oshiro and Otsuka pharmacologist Dr. Tsuyoshi Hirose.

I. Otsuka's Fact Witnesses

1. Dr. Yasuo Oshiro

Dr. Oshiro is the first named inventor on the '528 patent. He led the research effort at Otsuka that resulted in the discovery of aripiprazole.

Dr. Oshiro joined Otsuka in 1974. He has been employed there ever since and currently holds the position of Advisor. In this position, he responds to scientific questions within Otsuka concerning the central nervous system, medicinal chemistry and drug design. [Tr. 1746-7 (Oshiro)]

The Court found Dr. Oshiro to be highly knowledgeable concerning the research leading to the discovery of aripiprazole and considered Dr. Oshiro to be a credible witness.

2. Dr. Tsuyoshi Hirose

Dr. Hirose is a pharmacologist employed by Otsuka. Dr. Hirose submitted a declaration to the U.S. Patent and Trademark Office ("PTO") during the reexamination proceedings relating to the '528 patent. That declaration included test data showing the superior properties of aripiprazole and certain other claimed compounds compared to structurally similar prior art compounds. [PTX 20]

Dr. Hirose currently holds the position of leader of the Aripiprazole Group at Otsuka. As leader of the Aripiprazole Group, he plans and performs testing concerning the pharmacological properties of aripiprazole. He also compiles test data concerning aripiprazole for presentations at scientific conferences. He additionally attends meetings of physicians in order to educate them about the proper use of aripiprazole and new activities of aripiprazole. [Tr. 1905-6 (Hirose)] Dr. Hirose also has published his work concerning aripiprazole in scholarly journals. [Tr. 1911-13 (Hirose)]

Dr. Hirose has worked in Otsuka's Aripiprazole Group since 1997. When Dr. Hirose first joined that group, he assisted with the preparation of world-wide regulatory submissions concerning aripiprazole, including the assembly of basic preclinical pharmacological data concerning aripiprazole for those submissions. Dr. Hirose gathered and accumulated pharmacological data and also performed supplemental pharmacological experiments in order to generate a data package for submission to regulatory authorities. This data package included anti-apomorphine stereotypy testing and Dr. Hirose assisted in the design and conduct of those experiments. This data package was submitted to various regulatory authorities, including the FDA. [Tr. 1908-11 (Hirose)]

The Court found Dr. Hirose to be knowledgeable about pharmacology, including aripiprazole's pharmacology. The Court considered Dr. Hirose to be a credible witness.

J. Otsuka's Expert Witnesses

1. Dr. Bryan Roth

The Court accepted Otsuka's expert witness, Dr. Bryan Roth, as a qualified expert in schizophrenia, antipsychotic drug discovery, and psychopharmacology with its medicinal chemistry component. [Tr. 1019 (Roth)]

Dr. Roth is a professor at the University of North Carolina-Chapel Hill. He is the Michael Hooker Distinguished Professor of Pharmacology and also holds the position of professor in the division of Medicinal Chemistry and Natural Products. Dr. Roth has secondary appointments in the Department of Psychiatry, the Division of Neurosciences, the Lindeberger Cancer Center and the Division of Toxicology. [Tr. 1001-02 (Roth); PTX 400]

Prior to joining the faculty at the University of North Carolina-Chapel Hill in 2006, Dr. Roth was a Professor of Psychiatry at Case Western Reserve University Medical School. He also had a secondary appointment in the Division of Neurosciences at Case Western Reserve University. [Tr. 1005 (Roth)]

Dr. Roth practiced medicine as a psychiatrist for more than ten years while he was teaching at Case Western. His clinical practice was devoted to treating patients with schizophrenia. [Tr. 1005 (Roth)] In his medical practice, Dr. Roth treated thousands of persons with schizophrenia at the University Hospitals. He typically would see 15 to 20 schizophrenia patients per day. He did that seven days a week for more than ten years. [Tr. 1007 (Roth)]

Dr. Roth's research efforts at Case Western University were devoted to understanding the pharmacology of antipsychotic medications. While at Case Western University, Dr. Roth also participated in clinical trials to evaluate potential new antipsychotic drugs at the University Hospitals. He tested nearly all of the compounds that subsequently became approved atypical antipsychotic drugs when they were still numbered compounds from the pharmaceutical companies. He also evaluated many numbered compounds that, for one reason or another, failed as treatments for schizophrenia. [Tr. 1007-1008 (Roth)]

Dr. Roth's current research at the University of North Carolina remains devoted to schizophrenia and antipsychotic drugs. Part of his research seeks to discover new antipsychotic drugs to treat schizophrenia. [Tr. 1009 (Roth)] Dr. Roth has two large research programs funded by the National Institute of Mental Health. He is the principal investigator of the National Cooperative Drug Discovery Group, which is a collaboration between the University of North Carolina, Duke University, and Pfizer Pharmaceuticals. That group seeks to understand how aripiprazole works and, based on that understanding, to develop new antipsychotic drugs. Dr. Roth has conducted extensive scientific research relating to aripiprazole in connection with that program. [Tr. 1009-1010 (Roth)]

In addition, for the last thirteen years Dr. Roth has run the National Institute of Mental Health Psychoactive Drug Screening Program, which is a research program devoted to psychiatric drug discovery. Over the past ten years, Dr. Roth and his colleagues have screened hundreds of thousands of compounds in that program. [Tr. 1009-1010 (Roth)]

During Dr. Roth's long and distinguished career, he has developed expertise in all aspects of schizophrenia, antipsychotic drugs, and antipsychotic drug development.

Dr. Roth has extensive experience in human clinical trials of potential antipsychotic drugs. He has conducted clinical trials, examined and interpreted the results of clinical trials, and helped to design clinical trials for pharmaceutical companies. He has consulted with pharmaceutical companies on the interpretation of their clinical study results. Dr. Roth also has consulted with the FDA on the serious side effects of antipsychotic medications. [Tr. 1011 (Roth)]

Dr. Roth also has extensive preclinical experience relating to antipsychotic drug discovery. He has been involved in the earliest stage of drug discovery, molecular target identification, all the way through pharmacologic profiling, medicinal chemistry, preclinical toxicology, and preparation of data for submission of an Investigational New Drug (IND) application to the FDA. [Tr. 1011 (Roth)] Dr. Roth has designed preclinical studies using behavioral screening tests in rodents. He has addressed blinding issues in his study designs. On a daily basis, Dr. Roth analyzes the results of behavioral screening tests in connection with his own research as well as the research of other groups for whom he has consulted. [Tr. 1013 (Roth)] Dr. Roth also has extensive experience with radioligand binding assays. [Tr. 1012 (Roth)]

Dr. Roth has consulted extensively on the subject of antipsychotic drug discovery for major pharmaceutical companies and charitable groups. He has consulted on both preclinical and clinical aspects of antipsychotic drug discovery. [Tr. 1014 (Roth)]

Dr. Roth has served on advisory panels of the National Institutes of Health (NIH). He meets with the NIH several times a year to advise them on various subjects related to psychiatric drug discovery and basic research related to psychiatry. [Tr. 1012 (Roth)]

Dr. Roth has published close to 300 peer-reviewed scientific papers, many of which relate to aripiprazole or other antipsychotic drugs. [Tr. 1013-1014 (Roth)] Dr. Roth has given more than 200 invited lectures on antipsychotic drugs and related subjects. [Tr. 1014 (Roth)]

Dr. Roth has served as a member of the editorial board of major pharmacology journals. He is an associate editor of the Journal of Pharmacology and Experimental Therapeutics, which is the official journal of the American Society of Pharmacology and Experimental Therapeutics. He has served on the editorial boards of Molecular Pharmacology, Psychopharmacology, Neuropsychopharmacology, Medicinal Chemistry Research, Medicinal Chemistry Letters, the Journal of Biological Chemistry, the Journal of Neurochemistry, and the Journal of Receptors and Signal Transduction Research. [Tr. 1015 (Roth)] Dr. Roth has served as an editorial referee for major scientific journals, including Science, Nature, and Neuron. He was a guest editor for the Proceedings of the National Academy of Sciences. [Tr. 1016 (Roth)]

Dr. Roth is an inventor on patents relating to potential antipsychotic drugs. His patents have been licensed out to pharmaceutical companies. [Tr. 1016-1017 (Roth)]

Dr. Roth has received a number of honors and awards for his schizophrenia research. He received the NARSAD Distinguished Investigator Award from the National Alliance for Research in Schizophrenia and Depression, which is the largest charitable organization that funds research related to schizophrenia. Dr. Roth has also received several named lectureships. [Tr. 1017-1018 (Roth)]

2. Dr. David E. Nichols

The Court accepted Otsuka's expert, Dr. David E. Nichols, as a qualified expert in medicinal chemistry and pharmacology. [Tr. 1519 (Nichols)]

Dr. Nichols is the Robert C. and Charlotte P. Anderson Distinguished Chair in pharmacology at Purdue University. He is also a distinguished professor of medicinal chemistry and molecular pharmacology at Purdue. [PTX 108] Dr. Nichols has taught at Purdue since November 1974. [Tr. 1504-1505 (Nichols)] Dr. Nichols also holds an adjunct appointment as a professor of pharmacology in the Indiana University School of Medicine. [Tr. 1505 (Nichols)]

Dr. Nichols has authored about 275 publications, including peer-reviewed scientific papers, book chapters, and monographs. His publications bridge the fields of medicinal chemistry and pharmacology. In his published papers that include biological data, most often the biological data are generated in his own laboratory. [Tr. 1515 (Nichols)]

Dr. Nichols's overarching research interest is understanding the role of biogenic amines in behavior. Biogenic amines include serotonin, dopamine, and norepinephrine. Dr. Nichols also studies the relationship between a molecule's structure and its ability to affect biological functions. [Tr. 1509 (Nichols)]

Dr. Nichols has pursued two parallel research tracks, one involving the study of dopamine systems, and the other involving the study of serotonin systems, particularly the 5-HT_{2A} serotonin receptor system. [Tr. 1509 (Nichols)] Dr. Nichols's serotonin research, which focused on hallucinogens that activate that receptor, was funded by the National Institute on Drug Abuse. His dopamine research is funded by the National Institute of Mental Health. [Tr. 1509-1510 (Nichols)]

Dr. Nichols has performed research related to potential treatments for schizophrenia. In the 1980s, he had a joint grant to attempt to develop dopamine autoreceptor agonists as novel therapeutics for schizophrenia. Dr. Nichols also had a grant to investigate dopamine D_1 receptor ligands, which were thought at the time to represent potential novel drugs for schizophrenia. [Tr. 1513 (Nichols)]

Dr. Nichols discovered that D_1 agonists may improve the memory and cognitive deficits in schizophrenia patients. One of the compounds Dr. Nichols discovered in those research efforts is now being evaluated in clinical trials for that effect in schizophrenia. [Tr. 1514-1515 (Nichols)]

Dr. Nichols has published research relating to aripiprazole. He has investigated aripiprazole's behavioral properties in a rat assay and demonstrated that it is a potent serotonin $5HT_{1A}$ agonist. More recently, he has used aripiprazole as a test compound in published research seeking to develop his rat model of schizophrenia. [Tr. 1515-1516 (Nichols)]

Dr. Nichols is an inventor on several U.S. patents, including patents concerning his discovery of dopamine D_1 agonists. Dr. Nichols developed the first high-potency full D_1 agonist, which is currently in clinical trials now in schizophrenia patients. [Tr. 1516 (Nichols)]

Dr. Nichols has served on study sections and government review panels relating to issues of medicinal chemistry and pharmacology. In view of his broad background in both medicinal chemistry and pharmacology, he is often asked to review large projects in which medicinal chemists and pharmacologists are working collaboratively. [Tr. 1513-1514 (Nichols)]

Dr. Nichols has also received numerous honors and awards recognizing his scientific accomplishments. Dr. Nichols was named the Irvine H. Page lecturer for the Serotonin Club. Dr. Nichols also received the Provost's Award at Purdue University for Outstanding Graduate Mentors. [Tr. 1517-1518 (Nichols)] Dr. Nichols was also elected to membership in the American College of Neuropsychopharmacology, which is an organization principally of academic researchers and clinicians who study affective disorders such as schizophrenia, depression, and anxiety. It is a relatively small organization and few medicinal chemists have been elected to membership. [Tr. 1519 (Nichols)]

3. Dr. Ronald Thisted

The Court accepted Dr. Thisted as an expert in biostatistics. [Tr. 1437 (Thisted)] Biostatistics is the area of statistics that focuses on aspects of experimental design, implementation of studies, and the analysis of data from studies in the areas of biology and medicine. [Tr. 1431 (Thisted)]

Dr. Thisted is Chairman of the Department of Health Studies at the University of Chicago. The Department of Health Studies is responsible for biostatistics, epidemiology and health services research. Dr. Thisted is also Professor in the Department of Health Studies, Professor in the Department of Statistics, and Professor in the Department of Anesthesia and Critical Care. Dr. Thisted is a member of the Committee on Clinical Pharmacology and Pharmacogenomics. He is also the scientific director of the Biostatistics Core Facility of the University's Comprehensive Cancer Research Center. In addition, for the last 11 years he has served as co-director of the Clinical Research Training Program. [Tr. 1429 (Thisted); PTX 556]

Dr. Thisted's research is directed to computation and the design, execution and analysis of preclinical and clinical studies. [Tr. 1430-31 (Thisted)]

Dr. Thisted has published approximately 100 original articles in the peer-reviewed literature. He has published a book on statistical computation, a number of book chapters, book reviews, essays, and several pieces of computer software. He has also served on the editorial board of Transactions on Mathematical Software, on the Journal of Scientific and Statistical Computing of the Society for Industrial and Applied Mathematics, and he has been an associate editor of the Journal of the American Statistical Association, as well as editing for five years the Current Index to Statistics, which is an index to the worldwide literature in statistics. [Tr. 1434 (Thisted)]

Since the late 1970s, Dr. Thisted has consulted regularly with pharmaceutical companies in the areas of study design and data analysis as part of their drug development programs. He has been responsible for the statistical aspects of the design of preclinical and clinical trials for new drugs. He also has provided advice on the statistical design of preclinical and clinical studies. His advice on these studies has concerned a variety of matters including the selecting of the population of subjects to be studied, the number of subjects to be studied, the manner in which treatments or interventions are applied, aspects of blinding or randomization, the follow-up schedules and evaluation of measurements, the precision with which measurements are made, as well as planning the statistical analysis of the data that are collected and how those analyses will apply to answering the underlying question. [Tr. 1434-35 (Thisted)]

4. John C. Jarosz

The Court accepted Mr. Jarosz as an expert in the fields of economics and intellectual property valuation. [Tr. 2002 (Jarosz)]

Mr. Jarosz is an economist who specializes in the evaluation and valuation of intellectual property rights across various industries. Mr. Jarosz is currently a managing director of Analysis Group, Incorporated ("Analysis Group"), and the founder and director of their Washington, D.C. Office. Analysis Group is an economic strategy and financial consulting firm of about 500 people that assists clients in business, regulatory, and litigation settings. Analysis Group works in a variety of areas, including pharmacoeconomics and intellectual property evaluation and valuation. [PTX 345; Tr. 1996-8 (Jarosz)]

Mr. Jarosz received a B.A. in economics and organizational communication from Creighton University. Mr. Jarosz also attended law school and received a J.D. from the University of

Wisconsin. Although Mr. Jarosz has graduate training in both law and economics, he functions as an economist. [PTX 345; Tr. 1998-9 (Jarosz)]

Mr. Jarosz has worked for the pharmaceutical industry, in both litigation and non-litigation settings. Over the last several years, Mr. Jarosz has worked on 20 or more pharmaceutical assignments, including products covering a wide spectrum of illnesses and diseases. Mr. Jarosz has provided trial testimony on 45 or 50 occasions, including in the District of New Jersey about a dozen times over the years. [PTX 345; Tr. 1999-2001 (Jarosz)]

Mr. Jarosz is a member of many professional organizations and associations, including the American Economic Association, the American Law and Economics Association, the American Intellectual Property Law Association, the Intellectual Property Owners Association, and the Licensed Executive Society. [PTX 345; Tr. 2001-2 (Jarosz)]

K. Defendants' Expert Witnesses

1. Defendants' Expert Witnesses Lacked the Credentials and Expertise of Otsuka's Expert Witnesses

None of Defendants' expert witnesses has conducted any scientific research relating to aripiprazole. In contrast, both Dr. Nichols and Dr. Roth have studied aripiprazole.

None of Defendants' expert witnesses is a medical doctor, has any medical expertise relating to schizophrenia, or has any expertise in the evaluation of clinical study results. In contrast, Dr. Roth is a medical doctor with first-hand experience in evaluating and treating patients suffering from schizophrenia. Dr. Roth also has extensive expertise in evaluating clinical studies.

Defendants' expert witnesses have limited experience in antipsychotic drug development. Dr. Press was the only expert testifying for Defendants with any experience in antipsychotic drug

development, but that experience was primarily based on his research in the 1970s on clozapine analogs. In contrast, Dr. Nichols and Dr. Roth have extensive expertise in antipsychotic drug discovery and continue their research in this area today.

Defendants' experts also lacked expertise in statistics and economics. In contrast, Dr. Thisted is an expert biostatistician, and Mr. Jarosz is an expert economist.

a. Dr. Neal Castagnoli

Dr. Castagnoli is a chemist who has studied the interaction of monoamine oxidase and other brain enzymes and receptors with respect to neuroprotection and neurotoxicity in the central nervous system. He lacks any expertise or experience in the field of antipsychotic drug discovery. Dr. Castagnoli admitted on cross-examination that he has never personally discovered or attempted to discover a new antipsychotic drug. [Tr. 818 (Castagnoli)] Dr. Castagnoli has never developed an FDA-approved drug product of any kind. [Tr. 818 (Castagnoli)]

Dr. Castagnoli is not a medical doctor and is not capable of diagnosing a person suffering from schizophrenia. He also has never observed in a clinical setting a person suffering from schizophrenia. [Tr. 830 (Castagnoli)] Dr. Castagnoli is not a pharmacologist. He is not an expert in animal behavioral screening tests for antipsychotic drugs. [Tr. 879-80 (Castagnoli)]

Dr. Castagnoli has never designed a clinical study for an antipsychotic drug or participated in the conduct of a clinical trial for an antipsychotic drug. [Tr. 829-30 (Castagnoli)]

Dr. Castagnoli is therefore unqualified to offer expert testimony on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, animal models used to identify potential antipsychotic drugs, pharmacology (including clinical or behavioral

pharmacology), statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, or objective evidence of nonobviousness).

b. Dr. Jeffrey Press

Dr. Press is a patent litigation consultant with a chemistry background. Dr. Press has testified as an expert at trial or by deposition in approximately four patent cases over the last four years. In each of those cases, Dr. Press testified on behalf of the party challenging the patent. [Tr. 194-195 (Press)]

Dr. Press has no expertise in the area of brain pharmacology. [Tr. 193 (Press)] His limited experience in antipsychotic drug research ended more than 25 years ago. He last performed antipsychotic drug research at the bench in the late 1970s. [Tr. 194 (Press)] Dr. Press was not actively involved in antipsychotic research in 1988 and is not presently engaged in any scientific research related to antipsychotic drugs. [Tr. 194 (Press)]

Dr. Press is not a psychiatrist or medical doctor of any kind. [Tr. 281 (Press)] He has never taught in any university or medical school any course relating to schizophrenia or treatments for schizophrenia. [Tr. 281-282 (Press)] Dr. Press has never observed in a clinical setting a patient experiencing any adverse side effects caused by an antipsychotic medication. [Tr. 281 (Press)] He has never diagnosed or treated a patient suffering from schizophrenia or carried out a clinical trial to evaluate the efficacy or safety of a potential antipsychotic. [Tr. 281 (Press)] Dr. Press has never reviewed the results of a clinical trial for the purpose of advising a company whether to continue development of a potential antipsychotic drug. [Tr. 281 (Press)] The FDA has never requested Dr. Press's advice on clinical studies relating to a potential new antipsychotic drug. [Tr. 282 (Press)]

Dr. Press is therefore unqualified to offer expert testimony on psychiatry, neurobiology, schizophrenia, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, animal models used to identify potential antipsychotic drugs, pharmacology (including clinical or behavioral pharmacology), statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, and objective evidence of nonobviousness). Dr. Press is also unqualified to give expert testimony concerning economic and legal matters. [Tr. 175 (Press)]

c. Dr. Richard Beninger

Dr. Beninger is a psychologist who has used rats to study the role of neurotransmitters in reward-related incentive learning. [Tr. 914-915 (Beninger)] Dr. Beninger lacks any expertise or experience in the field of antipsychotic drug discovery. [Tr. 919 (Beninger)] Dr. Beninger is not a medicinal chemist. [Tr. 919 (Beninger)] He is not an expert in statistics or biostatistics. [Tr. 959-960 (Beninger)] Dr. Beninger is not a psychiatrist or medical doctor of any kind. He is therefore unqualified to offer expert testimony on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, medicinal chemistry, clinical pharmacology, statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, and objective evidence of nonobviousness).

d. Dr. John Marshall

Dr. Marshall is a neuroscientist who has used animal models to study the capacity of the central nervous system to regenerate following injury. He is not a medicinal chemist or a pharmacologist. [Tr. 714 (Marshall)] Nor is he a statistician. [Tr. 714 (Marshall)] Dr. Marshall has never developed a new drug of any kind, including an antipsychotic drug. [Tr. 713-714 (Marshall)] Dr. Marshall has no experience with the synthesis and design of potential neuroleptic drugs. [Tr. 716-718 (Marshall)]. Further, Dr. Marshall lacks any experience with the design and implementation of preclinical animal model screening programs for new drug development, including the development of new antipsychotic drugs. [Tr. 721 (Marshall)] Dr. Marshall has never diagnosed or treated a patient suffering from schizophrenia. [Tr. 723 (Marshall)] He has also never designed a clinical study for a new drug, including for an antipsychotic drug. [Tr. 721 (Marshall)] Dr. Marshall has never carried out a clinical trial to evaluate the efficacy or safety of a potential antipsychotic and has no experience evaluating test results from such a clinical trial. [Tr. 721-723 (Marshall)]

Dr. Marshall is therefore unqualified to offer expert testimony on psychiatry, human neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, medicinal chemistry, animal models used to identify potential antipsychotic drugs, clinical pharmacology, statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, or objective evidence of nonobviousness).

e. Mr. John Goolkasian

Mr. Goolkasian is a patent attorney who holds an undergraduate degree in chemical engineering and no advanced technical degree. Mr. Goolkasian is not a psychiatrist (or medical doctor of any kind), medicinal chemist, pharmacologist, or statistician, and he lacks any expertise or experience in the field of antipsychotic drug discovery. In particular, he has no experience in the field of medicinal chemistry as related to antipsychotic drug discovery. [Tr. 471-472 (Goolkasian)] He is therefore unqualified to offer expert testimony on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, medicinal chemistry, animal models used to identify potential antipsychotic drugs, pharmacology (including clinical or behavioral pharmacology), statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, or objective evidence of nonobviousness). Mr. Goolkasian is also unqualified to give expert testimony concerning the materiality of any information allegedly withheld from or misrepresented to the PTO during the prosecution or reexamination of the '528 patent or any alleged intent to deceive the PTO.

III. GENERAL FINDINGS OF FACT

A. Schizophrenia

Schizophrenia is a debilitating mental illness that affects approximately one-percent of the human population. [Tr. 1033-1034 (Roth); PTX 86] It is the most serious psychiatric disease. [Tr. 1034 (Roth)] Schizophrenia frequently strikes people in their late teens to early 20s and renders them essentially disabled for life. [Tr. 1034 (Roth)]

Despite extensive research, the cause, mechanism, and etiology of schizophrenia were unknown in 1988 and remain unknown today. [Tr. 1552 (Nichols); Tr. 1033 (Roth)] Researchers believe that both genetic and environmental factors may play a role in the cause of the illness. [Tr. 1033-1034 (Roth)]

Individuals with schizophrenia suffer from positive symptoms, negative symptoms, and cognitive deficits. [Tr. 1035 (Roth)] The positive symptoms of schizophrenia include hallucinations, delusions, and formal thought disorders. [Tr. 1035 (Roth)] Hallucinations are perceptual experiences for which there is no objective sensory input. [Tr. 1035 (Roth)] An individual with schizophrenia actually hears or sees things that are not there. [Tr. 1035-1036 (Roth)] Delusions are fixed false beliefs; for example, a person with schizophrenia may believe the CIA is spying on them. [Tr. 1035-1036 (Roth)] Formal thought disorders involve disorganized or illogical thinking. An individual with schizophrenia may experience "thought blocking" or "thought withdrawal" in which they lose thoughts, or "thought insertion" in which they experience unusual thoughts. [Tr. 1036-1037 (Roth)] One of Dr. Roth's patients, for example, would experience the unusual inserted thought to "buy Safeway spinach," which would cause him to believe that he needed to go out and buy Safeway spinach. [Tr. 1037 (Roth)]

The positive symptoms of schizophrenia can be completely debilitating for the individual with schizophrenia. [Tr. 1037 (Roth)] The typical patient with schizophrenia is unemployable for life. [Tr. 1037 (Roth)] Persons with schizophrenia "lack insight" with respect to their positive symptoms, meaning they do not know that what they are experiencing is not real. [Tr. 1037-1038 (Roth)]

The negative symptoms of schizophrenia (also called "deficit symptoms") include flat or inappropriate affect. [Tr. 1040 (Roth)] An individual with flat affect shows no emotion whereas

someone with inappropriate affect may laugh at something that is frightening or sad. [Tr. 1040-41 (Roth)] Negative symptoms also include decreased motivation, social withdrawal, and a failure to pick up on social cues. [Tr. 1041 (Roth)]

Cognitive deficits are reflected in a typical loss of 10 to 20 IQ points in persons with schizophrenia as well as a disturbance of executive functions. [Tr. 1041-1042 (Roth)]

Dr. Roth has personally observed all of the symptoms of schizophrenia in his patients. [Tr. 1042 (Roth)] None of Defendants' experts are psychiatrists or medical doctors of any kind or have any significant experience with schizophrenia patients. [Tr. 281 (Press); DTX 1441; Tr. 723 (Marshall); DTX 1431; DTX 1428]

B. The First-Generation Antipsychotics

The first antipsychotic drug, chlorpromazine, was discovered by accident in the early 1950s. [Tr. 1126-1127 (Roth)] After chlorpromazine was discovered, researchers determined that its antipsychotic properties were due to its antagonism (blockade) of dopamine receptors in the brain. [Tr. 1126 (Roth)] That key finding led to the development of other "typical" antipsychotics, including haloperidol, thiothixene, trifluoperazine, fluphenazine, thioridazine, mesoridazine, loxapine, molindone, perphenazine, and pentoxide. [Tr. 1127-28 (Roth); Tr. 1532-1533 (Nichols)]

Although typical antipsychotic drugs often treat the positive symptoms of schizophrenia, they cause a number of undesirable side effects, including extrapyramidal side effects ("EPS"). [Tr. 1144 (Roth)] Extrapyramidal side effects include drug-induced Parkinsonism, which is a syndrome that is virtually indistinguishable from Parkinson's disease. Individuals with EPS may have a resting tremor, a shuffling gait, and a stiff, masklike expression. [Tr. 1144 (Roth)] Typical antipsychotics also cause acute dystonic reactions, which are involuntary contractures of voluntary muscle groups

in the body, or akathisia, which is a feeling of inner restlessness that may cause a patient to rock back-and-forth. [Tr. 1144-1145, 1147 (Roth)]

Typical antipsychotics may also cause tardive dyskinesia, which is a late-occurring extrapyramidal side effect. [Tr. 1144-1145 (Roth)] Tardive dyskinesia generally occurs weeks, months, or even years after treatment with typical antipsychotics. [Tr. 1145 (Roth)] It may be irreversible if a patient stays on a typical antipsychotic drug. [Tr. 1145 (Roth)] As illustrated by a video shown during trial, severe tardive dyskinesia may make it difficult for a patient to even walk. [Tr. 1145-1148 (Roth)]

Prolactin is a hormone produced in the pituitary gland. [Tr. 1148 (Roth)] Typical antipsychotics elevate prolactin levels because of their blockade of D_2 dopamine receptors. [Tr. 1148 (Roth)] Elevated prolactin levels can lead to expression of milk from the breasts (galactorrhea) in women and the enlargement of the breasts (gynecomastia) and impotence in men. [Tr. 1148-1149 (Roth)] Dr. Roth explained that many of his male patients stopped taking their antipsychotic medication due to the side effects caused by elevated prolactin levels. [Tr. 1148-1149 (Roth)]

Typical antipsychotics may also cause cardiovascular side effects, including orthostatic hypotension, tachycardia, frank hypotension, and an arrhythmia known as prolongation of the QT interval. [Tr. 1149 (Roth)] Certain typical antipsychotic drugs have a "black box" warning for prolongation of the QT interval. [Tr. 1149 (Roth)] At high doses, typical antipsychotics may have quinidine-like effects, which are arrhythmogenic effects. [Tr. 1149 (Roth)]

Orthostatic hypotension can be quite serious. [Tr. 1149-1150 (Roth)] A patient may hit his or her head and have a subdural hematoma, which can be fatal. [Tr. 1149 (Roth)] Elderly patients

in particular frequently fall and break their hip, which can lead to an early death. [Tr. 1149-1150 (Roth)]

The side effects of typical antipsychotics frequently lead patients to stop taking their antipsychotic medication or to not tolerate their medication. [Tr. 1150 (Roth)] In addition, typical antipsychotics generally worsen the negative symptoms of schizophrenia and have no effect on cognitive deficits. [Tr. 1144 (Roth)]

When he was a practicing psychiatrist, Dr. Roth prescribed all of the available typical antipsychotic drugs. [Tr. 1143-44 (Roth)] He personally observed the shortcomings of these medications when he treated schizophrenia patients. [Tr. 1150 (Roth)] Many patients were not adequately treated by typical antipsychotics or not treated at all. [Tr. 1150-51 (Roth)] Typical antipsychotics therefore were not fully satisfactory as drugs for the treatment of schizophrenia in the 1980s. [Tr. 1150 (Roth)]

C. A Second-Generation Antipsychotic: Clozapine

Another breakthrough occurred with the discovery of clozapine. Clozapine was referred to as the first "atypical" antipsychotic drug because it treated schizophrenia without inducing EPS. [Tr. 1128-30 (Roth); Tr. 1533 (Nichols); Tr. 195 (Press)] It was initially evaluated clinically as a potential antipsychotic in the early 1970s. [Tr. 1129 (Roth)]

Clozapine has beneficial clinical properties besides its lack of EPS. [Tr. 1129-30 (Roth)] About 30 to 40 percent of patients with schizophrenia do not respond adequately to treatment with typical antipsychotics. [Tr. 1129 (Roth)] Clozapine is effective in many of those "treatment-resistant" patients. [Tr. 1129 (Roth)] Another group of patients cannot tolerate the side effects of

antipsychotic drugs, and clozapine is also effective in many of those "treatment-intolerant" patients. [Tr. 1129 (Roth)]

Clozapine has several potential adverse side effects including agranulocytosis, which occurs in about 0.7 percent of patients who are administered clozapine. [Tr. 1131 (Roth)] Agranulocytosis causes the patient to have a diminished neutrophil count. [Tr. 1131 (Roth)] Neutrophils are the white blood cells in the body that fight bacterial infection. [Tr. 1131 (Roth)] If agranulocytosis is not discovered in time, it may be fatal. [Tr. 1131 (Roth)]

Clozapine can induce seizures and frequently causes orthostatic hypotension or frank hypotension. [Tr. 1131 (Roth)] Its propensity to cause orthostatic or frank hypotension often is dose limiting, meaning the physician cannot give the patient a therapeutic dose of the drug. [Tr. 1131-1132 (Roth)]

Clozapine was withdrawn from clinical trials in the 1970s after it was discovered to cause agranulocytosis in some patients. [Tr. 1133 (Roth); Tr. 196 (Press)] Clozapine was eventually approved as an antipsychotic drug in the United States in 1990, but only for treatment-resistant or treatment-intolerant schizophrenia patients. [Tr. 1136-37 (Roth)] Its use was also subject to strict blood-monitoring requirements. [Tr. 1133-34, 1136-37 (Roth)] Clozapine was therefore not generally available to treat schizophrenia patients in the United States in October 1988 because it had not been approved by the FDA. [Tr. 1134 (Roth)]

D. Failures to Develop Improved Antipsychotics in the 1970s and 1980s

Following the discovery of clozapine's toxicity, scientists made extensive efforts in the late 1970s and 1980s to develop improved antipsychotic drugs. [Tr. 1134-35 (Roth)] They sought to develop clozapine-like atypical antipsychotics with less toxicity and fewer side effects. [Tr. 1591-92

(Nichols)] Those research efforts, however, were largely unsuccessful. [Tr. 1139-40 (Roth)] In fact, between 1976 and 1989, no new antipsychotic drugs were approved for marketing in the United States. [Tr. 1134-1136 (Roth); Tr. 1565 (Nichols); PTX 79]

These widespread failures to develop improved antipsychotics in the 1970s and 1980s were reported in the literature. [Tr. 1136-1140 (Roth); PTX 93; PTX 94] For example, a 1987 paper authored by Dr. Leo Hollister stated: "It is most discouraging that more effective pharmacotherapy for schizophrenia has not been developed in the more than three decades since the introduction of the first effective drugs." [Tr. 1138 (Roth); PTX 93] Dr. Hollister was one of the most preeminent clinical pharmacologists in the field of psychiatry during that time period. [Tr. 1137 (Roth)]

Otsuka established that numerous potential new antipsychotic drugs failed for a variety of reasons in the 1970s, 1980s, and beyond. [PTX 319; PTX 320; PTX 321; PTX 322; Tr. 1565-1588 (Nichols); PTX 113-123; PTX 125-131; PTX 133-170; PTX 175; PTX 179-183; PTX 220; PTX 227-228; PTX 245; PTX 282-286; Tr. 1134-1140 (Roth)] Defendants never attempted to dispute this evidence of widespread failures.

Pursuant to 35 U.S.C. § 119, the '528 patent is entitled to a priority date of October 31, 1988. [Tr. 1591 (Nichols); Def. FOFCOL, page 2] As of that date, only first-generation antipsychotics such as chlorpromazine and haloperidol, having the serious shortcomings described above, were available to be prescribed to schizophrenia patients in the United States. [Tr. 1134, 1143 (Roth)]

E. The Challenges of Antipsychotic Drug Research

The extensive failures in antipsychotic drug discovery are due largely to the complexity and unpredictability of this area of research.

1. Brain Chemistry

As Defendants' expert Dr. Castagnoli candidly acknowledged, the "chemistry of the living system is extraordinarily complex." [Tr. 609 (Castagnoli)] That complexity is perfectly exemplified by the biochemistry of the human brain. Neurons, which transmit electro-chemical signals within and from the brain, are responsible for essentially all of the brain's functions. [Tr. 1020, 1030-1032 (Roth)] There are about 100 billion neurons in the brain interconnected by hundreds of trillions of synapses. [Tr. 1030 (Roth)]

Neurons communicate with each other through a process known as "neurotransmission." [Tr. 1030, 1021-1022 (Roth)] Neurotransmission occurs simultaneously in different parts of the brain and gives rise to all human thoughts, perceptions, muscle movements, senses, and emotions. [Tr. 1030 (Roth)]

Signal molecules called "neurotransmitters" cause changes within brain cells when they bind to specialized "receptors" on the surface of the cell. [Tr. 1025 (Roth)] Receptors are complex structures that interact with particular neurotransmitters to stimulate or modulate a particular physiological response. [Tr. 1533-1536 (Nichols)] Much of the effort related to the development of drugs for psychiatric disorders has been directed to finding new molecules, different from the natural transmitter molecules, that bind to and alter the function of receptors in the brain thought to be involved in a particular mental illness. [Tr. 1539-1541 (Nichols)]

Molecules that bind to a receptor can have two principal effects: They can be "agonists" that stimulate the physiological response of the receptor or "antagonists" that block or prevent the physiological response of the receptor. [Tr. 1021-1022, 1051-1052, 1056-1059, 1126-1127 (Roth)]

Hundreds of different neurotransmitters activate receptors in the brain, including dopamine, which activates "dopamine" receptors; serotonin, which activates "serotonergic" receptors; histamine, which activates "histaminergic" receptors; norepinephrine, which activates "adrenergic" receptors; and acetylcholine, which activates "cholinergic" (particularly a subtype called "muscarinic") receptors. [Tr. 1031-1032 (Roth); Tr. 1537 (Nichols)] In addition, there are numerous "subtypes" of each of these receptors. For example,"D_1" and "D_2" dopamine receptor subtypes and "5-HT_1" and "5-HT_2" serotonin receptor subtypes were known in 1988. [Tr. 1032-1033 (Roth); Tr. 1537-1539 (Nichols)]

2. The Complexity of Antipsychotic Drug Discovery

In 1988, researchers generally agreed that antipsychotic drugs work by blocking postsynaptic D_2 dopamine receptors. [Tr. 1533 (Nichols)] They also understood that antipsychotic drugs, especially atypical antipsychotics, interact with multiple receptors in the brain. [Tr. 1539-1541 (Nichols)] However, no consensus existed with respect to what was needed to create an atypical antipsychotic drug; instead, researchers proposed "theory after theory after theory, and no one really knows even today" what is needed for an atypical antipsychotic. [Tr. 1533, 1539-1541 (Nichols)] Thus, the discovery of new antipsychotic drugs in the 1980s was highly unpredictable. [Tr. 1552 (Nichols)]

Clozapine was found to have a remarkably complex pharmacology, interacting with dopamine receptors, serotonin receptors, histamine receptors, acetylcholine receptors, adrenergic receptors, and other receptors in the brain. [Tr. 1163-64 (Roth)] Precisely which of those receptors were involved in clozapine's "atypical" therapeutic action and what the optimal balance was between those receptors was unknown in the 1980s and remains unclear today. [Tr. 1533, 1535-1541, 1547-1550 (Nichols)]

The discovery of diverse receptor subtypes only further complicated research efforts. Thus, in 1988, schizophrenia researchers could only make "lots and lots of compounds, thousands of compounds" and test them in the hope of finding one that had the right balance of activity. [Tr. 1541 (Nichols)]

Molecules such as receptors or neurotransmitters have three-dimensional structures. [Tr. 1535-1536 (Nichols)] The three-dimensional structures of the different receptors in the brain were unknown in 1988 and remain unknown today. [Tr. 1533-1534, 1536 (Nichols)] The potential need for an antipsychotic drug to interact with two or more different receptors of unknown structure made the discovery of new atypical antipsychotic drugs a tremendous challenge. [Tr. 1533, 1540, 1547-1549 (Nichols)]

Schizophrenia researchers in the 1980s could not reliably predict from a compound's chemical structure whether it would be a safe, therapeutically effective atypical antipsychotic drug. [Tr. 1551-52 (Nichols)] For example, if a researcher had 100 different chemical structures sitting in front of him or her in October 1988, he or she could not have predicted the pharmacological properties of each structure. [Tr. 1140 (Roth)] Even today, researchers cannot look at the chemical structure of a potential drug and reasonably predict that the compound will treat the positive symptoms of schizophrenia without testing that compound in some accepted animal model of potential antipsychotic activity. [Tr. 1141 (Roth)] Defendants introduced no evidence to the contrary.

Changes in chemical structure can cause unpredictable changes in biological activity. [Tr. 1550-52 (Nichols)] Researchers found, for example, that simply moving the chlorine atom in clozapine from one side of the molecule to the other to make isoclozapine destroyed clozapine's atypical property. [Tr. 1554-56 (Nichols); PTX 288]

Tilozepine (also known as "NT 104-252") has the same tricyclic nucleus as clozapine, but includes a modified ring structure. [Tr. 1558-59 (Nichols)] It proved to be an effective antipsychotic with a rapid onset of action and rare extrapyramidal side effects; however, pro-convulsive effects were observed in preclinical tests and nine patients experienced epileptiform seizures in clinical trials. [Tr. 1560-1561 (Nichols); PTX 118] Clinical trials of tilozepine were therefore discontinued. [Tr. 1558-61 (Nichols); PTX 118]

Flumezapine also has the same tricyclic nucleus as clozapine, but includes a thiophene ring. [Tr. 1562 (Nichols)] In addition, the chlorine in clozapine is replaced with a fluorine in flumezapine. [Tr. 1562 (Nichols)] Flumezapine, however, was abandoned as a potential antipsychotic after it showed liver toxicity in clinical trials in humans. [Tr. 1562-65 (Nichols); PTX 280]

N-desmethylclozapine was developed as a clozapine-like potential antipsychotic. [Tr. 1173 (Roth)] Although it differs from clozapine only in the omission of a single methyl group on the piperazine ring, its pharmacology is completely different from clozapine. [Tr. 1173 (Roth)] N-desmethylclozapine was found to be ineffective in treating schizophrenia in clinical trials. [Tr. 1173 (Roth)]

After lack of efficacy, the next most common cause of failure of potential antipsychotic drugs is some undesirable "ADME/Tox" feature of the drug. ADME/Tox properties include a drug's absorption ("A"), distribution ("D"), metabolism ("M"), elimination ("E"), and toxicological ("Tox") properties. [Tr. 1141-1143 (Roth)] Toxicological properties include serious side effects that are typically associated with cell death or a cancer-inducing effect of the drug. [Tr. 1141-1143 (Roth)] Researchers cannot predict how small structural changes may affect a drug's ADME/Tox properties. [Tr. 1140-1141 (Roth)]

Thus, an antipsychotic drug must not only interact appropriately with all the relevant brain receptors to produce efficacy, it must not produce toxic effects in the periphery (e.g., in the liver, kidney, or blood cell-forming organs). [Tr. 1141-1143 (Roth); Tr. 1153-1154 (Nichols)] As Dr. Nichols explained: "So you've got this big balance. It's not just finding efficacy, finding something that works. You're also balancing that against all of the potential side effects and toxicity problems that could arise." [Tr. 1553-54 (Nichols)]

Schizophrenia researchers in the 1980s proposed several competing hypotheses to try to explain why clozapine is an atypical antipsychotic, and they used those hypotheses to guide their drug research. [Tr. 1164-1165 (Roth); Tr. 1533 (Nichols)] One such hypothesis, the anticholinergic hypothesis, had existed since the 1970s and remained prominent in 1988. [Tr. 1165 (Roth)] It proposed that clozapine's lack of EPS was due to its extremely potent anticholinergic activity. [Tr. 1165-1166 (Roth)] Aripiprazole does not fit within the anticholinergic hypothesis because it has essentially no affinity for cholinergic/muscarinic receptors. [Tr. 1166 (Roth)]

The serotonin-dopamine hypothesis arose from the discovery in 1974 that clozapine appeared to be a potent serotonin antagonist. [Tr. 1166 (Roth)] With the subsequent discovery of risperidone in 1987, scientists proposed that atypical antipsychotic drugs should have potent activity on 5-HT_2 serotonin receptors and low affinity for D_2 dopamine receptors. [Tr. 1166-1167 (Roth)] This was a powerful hypothesis that had emerged by 1988. [Tr. 1166-1167 (Roth)] Aripiprazole does not fit within the serotonin-dopamine hypothesis because it has higher affinity for D_2 dopamine receptors than for 5-HT_2 serotonin receptors, which is the *reverse* of the ratio proposed to be important according to the serotonin-dopamine hypothesis. [Tr. 1167 (Roth)]

The single molecular target hypothesis arose in the 1980s as a result of clozapine's rich pharmacology. [Tr. 1167 (Roth)] Researchers proposed that clozapine's atypicality may be due to its activity at one particular receptor target. [Tr. 1167 (Roth)] They did not know or agree, however, which receptor was the "key" to clozapine's atypicality and therefore developed compounds that were selective for various individual receptor targets such as D_1 dopamine receptors, sigma receptors, or certain serotonin receptor subtypes. [Tr. 1167-1168 (Roth)] A number of such selective compounds were tested prior to 1988. [Tr. 1167-1168 (Roth)] Aripiprazole does not fit within the single molecular target hypothesis because it has an exceedingly complex pharmacology. [Tr. 1168 (Roth)]

The limbic selectivity hypothesis was based on the idea that clozapine has activity at specific dopamine receptors found mainly in the limbic area of the brain. [Tr. 1168-1169 (Roth)] The idea was that one could make a drug that selectively targeted those dopamine receptors to make a clinically effective antipsychotic drug devoid of EPS. [Tr. 1169 (Roth)] Aripiprazole does not fit within the limbic selectivity hypothesis because it has affinity for dopamine receptors in all regions of the brain. [Tr. 1169 (Roth)]

Notably, each of these four major hypotheses of atypical antipsychotic drug action was based on some aspect of clozapine's pharmacology, showing the central role of clozapine in antipsychotic drug research in the 1980s. [Tr. 1169 (Roth)] It is also notable that none of these hypotheses would have led to aripiprazole. [Tr. 1166-1169 (Roth)]

The Court finds that creating an improved antipsychotic drug with a favorable side-effect profile was an extremely challenging endeavor in 1988 and remains so today. Otsuka's aripiprazole is one of only a handful of new antipsychotic drugs that have been developed and approved for marketing since 1975.

F. Otsuka's Discovery of Aripiprazole

Dr. Oshiro began his investigations which led to aripiprazole around 1985, when a superior requested that Dr. Oshiro write a paper about OPC-4392, a carbostyril compound discovered by other researchers at Otsuka as a potential antipsychotic drug. [Tr. 1748 (Oshiro)] In response to this request, Dr. Oshiro assembled the materials he was provided concerning OPC-4392 and also gathered textbooks and papers relating to antipsychotics and drugs to treat schizophrenia in order to study these subjects. [Tr. 1748-1749 (Oshiro)] Dr. Oshiro concluded through his review of these materials that OPC-4392 was going to fail as an antipsychotic drug, without a doubt. [Tr. 1749, 1802, 1807 (Oshiro)] This realization inspired Dr. Oshiro to search for a new compound with properties different from OPC-4392 that could be a successful antipsychotic drug. [Tr. 1750, 1807, 1831 (Oshiro)]

Dr. Oshiro had concluded that OPC-4392 would fail because it is an autoreceptor agonist. [Tr. 1749 (Oshiro)] Through his studies, Dr. Oshiro had determined that autoreceptor agonists, such as OPC-4392, cannot effectively treat the positive symptoms of schizophrenia. [Tr. 1749 (Oshiro)] Dr. Oshiro further concluded that, in order for any drug to treat the positive symptoms of schizophrenia, the drug must have dopamine D_2 receptor blocking activity. [Tr. 1749 (Oshiro)] For example, he noted that drugs known to treat schizophrenia, such as haloperidol and chlorpromazine, had the activity of blocking D_2 receptors. [Tr. 1749 (Oshiro)]

Dr. Oshiro completed the article concerning OPC-4392, and this paper was ultimately published in what was referred to at trial as the Banno article. [Tr. 1750 (Oshiro); Tr. 531-535 (Goolkasian); DTX 84] Dr. Oshiro did not include in that article, however, any of his conclusions regarding the inevitable failure of OPC-4392. [Tr. 1749-1750 (Oshiro)] His assignment was to

summarize the work of others, not his own, and thus the paper was not to reflect his own conclusions. [Tr. 1750 (Oshiro)]

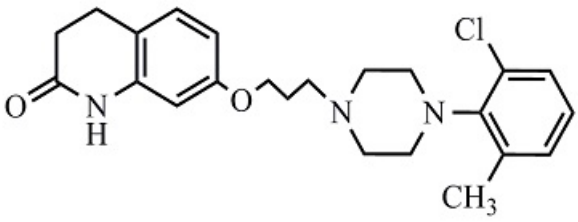
Having completed his work on this article, Dr. Oshiro determined that he had to begin from scratch to come up with a new compound different from OPC-4392 and having a different mechanism of action from that of OPC-4392. [Tr. 1750, 1807 (Oshiro)] To achieve this goal, he asked Otsuka individuals handling biology matters to come up with a testing system to evaluate the inhibition of apomorphine-induced stereotypy, i.e., D_2 receptor antagonist activity, in mice. [Tr. 1750 (Oshiro)] Dr. Oshiro focused on mice for several reasons, including his beliefs that carbostyril derivatives, including OPC-4392, were metabolized more quickly in rats, rats are larger animals and thus require a larger volume of the drug being examined and the variance in the data tends to be larger in rats. [Tr. 1751 (Oshiro)] Dr. Oshiro also thought that using mice would provide results closer to those obtained in humans. [Tr. 1751 (Oshiro)]

After the biology department developed the apomorphine-induced stereotypy inhibition test ("stereotypy test") in response to Dr. Oshiro's instructions, Dr. Oshiro requested that this test be conducted on haloperidol, which at that time had the strongest effect for D_2 receptor antagonist activity. He also requested that this test be conducted on chlorpromazine, which was the world's first drug used to treat schizophrenia. The foregoing testing confirmed that both haloperidol and chlorpromazine show strong activity in the stereotypy test. [Tr. 1751-52 (Oshiro)]

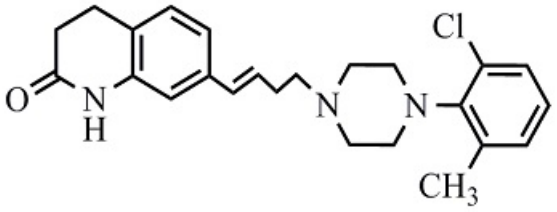
Dr. Oshiro also tested OPC-4392 in the stereotypy test. He had heard others at Otsuka report that OPC-4392 was weak in improving the positive symptoms of schizophrenia, but he concluded that the data more reliably showed that OPC-4392 actually worsened the positive symptoms of schizophrenia. [Tr. 1753-54, 1802 (Oshiro)] Dr. Oshiro therefore was interested in determining

whether the stereotypy test would confirm that OPC-4392 could not improve the positive symptoms. This testing did in fact confirm Dr. Oshiro's opinion that OPC-4392 did not have the pharmacological properties necessary to treat the positive symptoms of schizophrenia. [Tr. 1754, 1767-1769 (Oshiro); PTX 35; PTX 35T]

Based on the results of the foregoing testing, Dr. Oshiro concluded that he needed to discover a compound having the same level of activity in the stereotypy test as haloperidol. [Tr. 1755 (Oshiro)] He therefore requested that the Otsuka biology department search among Otsuka's stock of compounds known as the OPC-4000 series to find a compound having a stronger activity in the stereotypy test than chlorpromazine, at a minimum, and as close to haloperidol's level of activity as possible. [Tr. 1744 (Oshiro)] The 4000 series of compounds included various structurally different compounds, and he requested that the biology department randomly select compounds for testing. [Tr. 1755-56 (Oshiro)] They were unable to find any compounds having an activity close to haloperidol. [Tr. 1756 (Oshiro)] They did find, however, two seed compounds having activities in the stereotypy test stronger than OPC-4392 but not as strong as chlorpromazine. A seed compound is a compound having the targeted activity but at a level which is too weak for the compound to be developed as a drug but sufficient for the compound to be used for further research. [Tr. 1756 (Oshiro)] The seed compounds identified were OPC-4310 and OPC-4470. [Tr. 1756 (Oshiro); PTX 33 at OPC0768530; PTX 33-T at OPC0768530] OPC-4310 was mistakenly believed at that time to have the following structure:



[*Id.*] And OPC-4470 was mistakenly believed to have the following structure:



[*Id.*] Dr. Oshiro summarized the identification of these seed compounds in his monthly report prepared in October of 1986. [PTX 33; PTX 33-T]

Dr. Oshiro then proceeded to investigate a series of structural modifications to these seed compounds in an effort to discover a compound with enhanced potency in the stereotypy test. With respect to seed compound OPC-4310, Dr. Oshiro first investigated the impact on activity of changing the positioning of the propoxy linker. OPC-4310 has a propoxy linker attached at the 7-position on the carbostyril core. He investigated the effect of changing the propoxy linker location to the 5-position, 6-position and 8-position on the carbostyril core. [Tr. 1761 (Oshiro)] With respect to seed compound OPC-4470, he investigated the impact of changing the butenyl linker to a butyl linker. [Tr. 1761-62 (Oshiro)] Dr. Oshiro summarized his investigations in his monthly report for November of 1986. [PTX 34 at OPC0768534; PTX 34-T at OPC0768534; Tr. 1763-1764 (Oshiro)] His summary noted that OPC-4310 with the 7-position linker had the strongest activity, the 6-position modification of that compound had some activity and the 5-position and 8-position versions of that compound had very little activity. He represented this relationship as follows "7-position > 6-position >> 5 or 8-position." He used the ">>" symbol to report that the 6-position compound had considerably greater activity than the 5-position and 8-position compounds. [PTX 34-T at OPC0768534]

Having found that the 7-position resulted in the strongest activity for compounds having OPC-4310's structure, he investigated the impact on activity if the linker was fixed at that position but the length of that linker was changed. [Tr. 1765 (Oshiro)] In doing so, he found that changing the propoxy linker to a butoxy linker resulted in a compound known as OPC-14542 having unexpectedly strong activity, namely the activity in the stereotypy test increased 15-fold. [Tr. 1767 (Oshiro)] This was something that he did not expect at all. [Tr. 1767 (Oshiro)] He reported this finding in his monthly report for December of 1986. [PTX 35 at OPC076839-41; PTX 35T at OPC076839-41; Tr. 1767-1768 (Oshiro)] Specifically, he noted that "there was a dramatic 15-fold increase in the dopamine blocking action" when the "chain [linker] of OPC-4310 was extended from 3 to 4 [i.e., from propoxy to butoxy]." He further reported that "[t]his was totally unexpected." [Tr. 1770-1771 (Oshiro); PTX 35 at OPC0768541; PTX 35T at OPC0768541]

He also summarized in this report the research which led up to this unexpected finding, including the identification of OPC-4310 and OPC-4470 as seed compounds and the identification of the 7-position version of OPC-4310 as having the strongest activity. [Tr. 1767-68 (Oshiro); PTX 35; PTX 35T] In addition, he included a table in his report summarizing the results of his research and, among other things, how the activity of OPC-14542 in the stereotypy test compared to other compounds. Specifically, he showed through this table that OPC-14542 had an ED_{50} value of 0.3 milligrams per kilogram, which was appreciably lower than the ED_{50} values of 3.0 milligrams per kilogram for chlorpromazine, the ED_{50} value of 5.5 milligrams per kilogram for seed compounds OPC-4310 and OPC-4470 and the ED_{50} value of 9.3 milligrams per kilogram for OPC-4392. This table also showed that the trans form of OPC-14543 (reflecting a specific geometric arrangement of the molecule with respect to the double bond in the linker chain) had an ED_{50} value of 1.7 milligrams

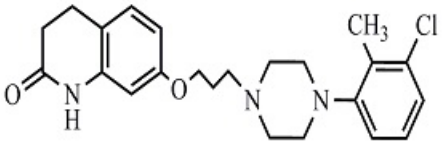
per kilogram, and he reported that they were conducting further investigations regarding cis compounds and alternative chain lengths. [Tr. 1767-1770 (Oshiro); PTX 35; PTX 35T]

Finally, this table in his report also provided data for the anti-epinephrine lethality test. This test reflects the propensity of the tested compounds to cause certain side effects, with larger numbers indicating fewer side effects. The ED_{50} value for haloperidol was >64 milligrams per kilogram, meaning that haloperidol had virtually no anti-epinephrine activity, whereas chlorpromazine had an ED_{50} value of 10.4 milligrams per kilogram, failed compound OPC-4392 had an ED_{50} value of 56.6 milligrams per kilogram, and the seed compounds OPC-4310 and OPC-4470 and the lead compound OPC-14542 had ED_{50} values of >128 milligrams per kilogram. [Tr. 1773-1775 (Oshiro); PTX 35T]

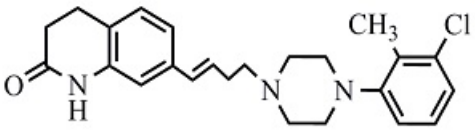
Dr. Oshiro also summarized in his report his investigation into whether changing the propoxy linker in OPC-4392 to a butoxy linker would produce the same unexpected 15-fold increase in stereotypy activity he had seen in making that change to OPC-4310. [Tr. 1772-73 (Oshiro); PTX 35; PTX 35T] He did not obtain the same level of increase and therefore did not analyze OPC-4392 further. [Tr. 1772-73 (Oshiro)] Instead, given the unexpected results with OPC-14542, Dr. Oshiro designated that compound as a lead compound for further research. A "lead compound" is one with enough activity without doing anything further to be moved forward into clinical trials. [Tr. 1773 (Oshiro)]

The next step after identifying OPC-14542 as a lead compound was to synthesize a large quantity of this compound for purposes of toxicity screening. [Tr. 1776 (Oshiro)] To do so, it was necessary to first synthesize a large quantity of the raw material used to produce the phenylpiperazine side chain. In the process of doing so, it was discovered that OPC-4310 and OPC-4470 did not have 2-chloro, 6-methyl substitutions on this side chain but rather 2-methyl, 3-chloro substitutions. This

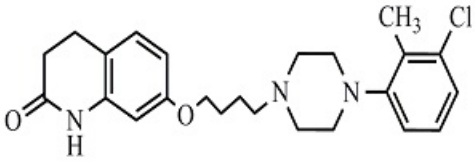
error was the result of an erroneous designation that appeared on the label of a raw material known as aniline. [Tr. 1776-78 (Oshiro)] Having discovered this error, it was confirmed that seed compounds OPC-4310 and OPC-4470 were actually 2-methyl, 3-chloro phenylpiperazine compounds, as was lead compound OPC-14542. [Tr. 1778 (Oshiro)] Dr. Oshiro reported the discovery of this error in his monthly report for February of 1987 and provided therein the following correct structures for OPC-4310, OPC-4470 and OPC-14542. [PTX 37; PTX 37T]



OPC-4310



OPC-4470



OPC-14542

Dr. Oshiro also summarized in this report his investigation into whether compounds having 2-chloro, 6-methyl substitutions would have any activity. OPC-14586 and OPC-14607 were synthesized, and it was found that these compounds did not have any activity to suppress apomorphine-induced stereotypy. [Tr. 1779 (Oshiro); PTX 37; PTX 37T]

Having identified the correct structure for the lead compound OPC-14542 as having substituents at the 2 and 3 positions of the phenylpiperazine ring, Dr. Oshiro investigated the impact of modifying the types of substituents at those positions. [Tr. 1779-80 (Oshiro)] His monthly report summarized a portion of that research and some of the additional compounds to be synthesized. [PTX 37; PTX 37T] The compounds being investigated included a variety of substituents (e.g., methyl, chlorine, bromine, ethoxy, fluorine) at both the 2 and 3 positions. Dr. Oshiro also investigated whether it would be possible to use the piperidinyl side chain present in strong D_2-blockers such as haloperidol and remperidol in place of the piperazinyl group in OPC-14542. The resulting compound, however, did not have any activity at all. [Tr. 1780-81 (Oshiro)]

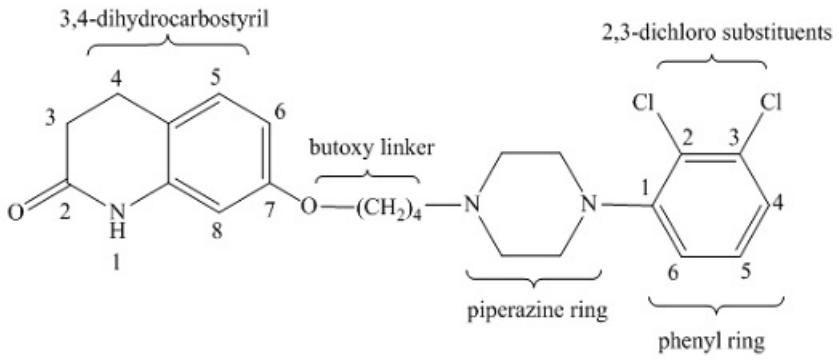
After additional research, Dr. Oshiro identified six compounds having promising pharmacological properties. [Tr. 1783-84 (Oshiro)] These compounds had post-synaptic D_2 receptor blocking activity. These compounds also had additional pharmacological properties, namely dopamine autoreceptor agonist activity and weak alpha-blocking activity. [Tr. 1783-84 (Oshiro)] Dr. Oshiro identified these compounds in his monthly report for March of 1987. [PTX 40; PTX 40T] These compounds were then tested in rats, and it was found that two of these compounds (designated OPC-14565 and OPC-14582) had diminished activity and thus were excluded from further research. [Tr. 1784 (Oshiro)]

Dr. Oshiro did not stop his research, however, after identifying these four compounds. Instead, he continued to evaluate other compounds having a variety of substituents in various combinations at various positions on the phenylpiperazine ring. Ultimately, he did not find any compounds preferable over the four reported in his March 1987 monthly report. [Tr. 1786 (Oshiro)] Those four compounds were then subjected to toxicity screening, and two of them (designated OPC-14542 and OPC-14597) were found to be safer and less toxic and thus were chosen for further research. [Tr. 1789-90 (Oshiro)]

Dr. Oshiro reported the results of the toxicity testing in his monthly report for July 1987. [PTX 47; PTX 47T] The next step in his research was to identify for each of those two compounds the minimum amount of compound required to show the desired activity and the maximum amount of compound that could be used before causing a toxic effect. [Tr. 1790 (Oshiro)] As a result of this testing, it was found that OPC-14597 had a superior effect as compared to OPC-14542 and also had a greater difference between the minimum effective dose and maximum toxic dose, and thus was a safer compound. [Tr. 1790 (Oshiro)] OPC-14597 was accordingly identified in Dr. Oshiro's monthly report for September of 1987 as being the compound to move forward with additional testing. [PTX 48; PTX 48T] Ultimately, OPC-14597 moved forward into clinical trials, was approved by the FDA and is now marketed in the U.S. as Abilify®. [Tr. 1791 (Oshiro)]

G. Aripiprazole's Unique Chemical, Pharmacological, and Clinical Properties

The chemical structure of aripiprazole is shown below:



Aripiprazole

[Uncontested Fact, Pretrial Stip. at ¶ 23]

As illustrated, aripiprazole includes a bicyclic system that for convenience is commonly referred to as the "carbostyril" portion of the molecule. [Uncontested Fact, Pretrial Stip. at ¶ 24] Because aripiprazole has two hydrogens at positions 3 and 4 of the carbostyril ring it is referred to as a "dihydrocarbostyril." Researchers commonly refer to both dihydrocarbostyrils and carbostyrils as "carbostyril derivatives." A dihydrocarbostyril has a single bond between positions 3 and 4 whereas a carbostyril has a double bond. [Tr. 1520-1522 (Nichols)] There is no other FDA-approved antipsychotic drug besides aripiprazole that is a carbostyril derivative. [Tr. 1522-1523 (Nichols); 1063-1064 (Roth); Tr. 191 (Press); Tr. 819 (Castagnoli)]

Aripiprazole is a 7-position carbostyril derivative with a butoxy linker. [Uncontested Fact, Pretrial Stip. at ¶¶ 25-26] There is no other FDA-approved antipsychotic drug besides aripiprazole that has a butoxy linker. [Tr. 1523-1524 (Nichols); 192 (Press); 819-20 (Castagnoli)]

Aripiprazole has a piperazine ring connected to the butoxy linker. The other side of the piperazine ring is connected to a phenyl ring. The phenyl ring includes chlorine substituents attached

at both the 2 position and 3 position of the phenyl ring. [Uncontested Fact, Pretrial Stip. at ¶ 27; Tr. 1524-25 (Nichols)] There is no other FDA-approved antipsychotic drug besides aripiprazole that includes a phenyl ring with chlorine substituents at both the 2 and 3 positions. [Tr. 1527 (Nichols); Tr. 192 (Press); Tr. 820 (Castagnoli)]

Looking at all of aripiprazole's structural features, there is no FDA-approved antipsychotic drug besides aripiprazole that is a carbostyril derivative with a butoxy linker and a phenyl ring having chlorine substituents at the 2 and 3 positions. [Tr. 1527 (Nichols); Tr. 193 (Press); Tr. 821 (Castagnoli)] Aripiprazole is thus chemically unique among the approved antipsychotic drugs. [Tr. 1527 (Nichols)]

A person of ordinary skill in the art in October 1988 would not have known the chemical structure of aripiprazole. [Tr. 1591 (Nichols)] Aripiprazole was not disclosed in any prior art reference as of the October 31, 1988, priority date of the '528 patent. [Tr. 1591 (Nichols)] Dr. Press testified that the '528 patent describes the chemical name of aripiprazole and that he had an understanding of the structure of aripiprazole. [Tr. 214 (Press)] When asked, "Had anything at all about aripiprazole been published by October 31, 1988?" Dr. Press replied, "Not to my knowledge." [Tr. 214 (Press)]

Dr. Roth testified that aripiprazole's pharmacology is both unique and exceedingly complex. [Tr. 1043 (Roth)] Aripiprazole, like other antipsychotic drugs, interacts with a large number of neurotransmitter receptors. [Tr. 1045 (Roth)] Dr. Roth has gained an understanding of aripiprazole's pharmacologic properties through his extensive scientific research and publications relating to aripiprazole. [Tr. 1009-10, 1014, 1043-44 (Roth); PTX 292; PTX 406] Defendants' experts, on the

other hand, appeared to have little or no understanding of aripiprazole's pharmacology. [*See, e.g.* Tr. 193 (Press); Tr. 712 (Marshall)]

As Dr. Roth explained, aripiprazole, unlike all other atypical antipsychotic drugs, has exceedingly high affinity for D_2 dopamine receptors and 5-HT_{1A} serotonin receptors. [Tr. 1048 (Roth)] The term "affinity" refers to how tightly a drug binds to a receptor. [Tr. 1047 (Roth)] The details of aripiprazole's receptor pharmacology are shown in a "heat map" in a 2004 publication authored by Dr. Roth concerning aripiprazole. [Tr. 1045-1048 (Roth); PTX 406] The heat map shows that aripiprazole interacts with many receptors and has varying affinities for each receptor subtype. [Tr. 1045-1048 (Roth); PTX 406]

Dr. Roth's heat map is useful in understanding aripiprazole's side effect profile and how it differs from that of other atypical antipsychotics. [Tr. 1048-1051 (Roth); PTX 406] It shows, for example, that aripiprazole has relatively low affinity for alpha-1 adrenergic receptors, which are responsible for causing orthostatic hypotension. [Tr. 1048-1049 (Roth); PTX 406] Aripiprazole also has low affinity for muscarinic receptors and therefore does not cause anticholinergic side effects such as dry mouth, constipation, and impaired cognition. [Tr. 1049-1050 (Roth); PTX 406] In addition, aripiprazole has relatively low affinities for H_1 histamine and 5-HT_{2C} serotonin receptors, which likely explains aripiprazole's relatively low propensity to cause weight gain compared to other antipsychotic medications. [Tr. 1048-50 (Roth); PTX 406] A person of ordinary skill in the art in October 1988 would not have known or been able to predict the pharmacological properties of aripiprazole. [Tr. 1060 (Roth); Tr. 1591 (Nichols]

Since aripiprazole was discovered, scientists have attempted to explain aripiprazole's pharmacologic properties using different terminology. [Tr. 1044 (Roth)] Aripiprazole has been

referred to as a partial agonist and has also been described as having functional selectivity. [Tr. 1052-1055 (Roth); PTX 292] Partial agonists can be distinguished from agonists and antagonists as follows. An agonist interacts with a receptor and activates it. [Tr. 1051-1052 (Roth)] An antagonist, on the other hand, binds to a receptor and occludes (blocks) the agonist binding site, preventing it from being activated. [Tr. 1051-1052 (Roth)] A partial agonist, however, fits into a receptor and activates it only to a certain extent. [Tr. 1052 (Roth)] It does not completely activate or inactivate the receptor, but instead provides a moderate degree of receptor activation. [Tr. 1052 (Roth)] Aripiprazole is unique among all antipsychotic drugs in that it can act as a partial agonist at D_2 dopamine receptors. [Tr. 1052 (Roth); Tr. 822 (Castagnoli); PTX 86; PTX 372]

As mentioned above, aripiprazole also exhibits "functional selectivity," meaning that its ability to activate or inactivate receptors depends on the receptor type, the local environment of the receptor, and the signaling event being measured. [Tr. 1053-1054 (Roth)] For example, at D_2 dopamine receptors, aripiprazole may act as an antagonist, a partial agonist, or a full agonist. [Tr. 1053-55 (Roth); PTX 292; PTX 86]

Dr. Roth first learned of aripiprazole at a 1994 meeting of the American College of Neuropsychopharmacology. [Tr. 1064-1065 (Roth)] He saw a poster that presented an abstract about aripiprazole. [Tr. 1064 (Roth)] Based on aripiprazole's purported mechanism of action, Dr. Roth was highly skeptical at that time that aripiprazole would be effective in treating schizophrenia. [Tr. 1065-1066 (Roth)] His skepticism changed, however, when he subsequently reviewed the Phase III clinical data at a meeting in Belgium several years later. [Tr. 1066-1067 (Roth)] It was clear to him from the Phase III clinical data that aripiprazole was effective in treating schizophrenia. [Tr. 1066 (Roth)] Dr. Roth decided at that time to begin investigating why aripiprazole is a therapeutically

effective atypical antipsychotic drug and his research along those lines continues today. [Tr. 1064-1067, 1009 (Roth)]

Aripiprazole was approved as an atypical antipsychotic in 2002. [Tr. 2062 (Jarosz); PTX 357 at OPC0806307] Aripiprazole has a number of clinical advantages over typical antipsychotics and other atypical antipsychotics in treating persons with schizophrenia. [Tr. 1151 (Roth)] Compared to the typical antipsychotic drugs, aripiprazole has a reduced propensity to induce extrapyramidal side effects or the late-occurring tardive syndromes such as tardive dyskinesia. [Tr. 1152 (Roth); PTX 86]

Aripiprazole also has a lower risk of cardiovascular side effects such as orthostatic hypotension or prolongation of the QT interval on the electrocardiogram. [Tr. 1152 (Roth); PTX 357 at OPC0806298; PTX 86] It is also less sedating and does not induce agranulocytosis under routine use. [Tr. 1152 (Roth)]

Importantly, aripiprazole has a lower risk of weight gain and associated metabolic side effects, which can include diabetes. [Tr. 1152 (Roth); PTX 357 at OPC0806298; PTX 86] Weight gain has been known to be a problem for many patients on antipsychotic drugs since at least the 1960s. [Tr. 1152 (Roth); PTX 294] Weight gain has become a more prominent problem in the last five to ten years because certain atypical antipsychotic drugs can cause substantial weight gain. [Tr. 1152-53 (Roth); PTX 294] It is not uncommon for patients on atypical antipsychotic drugs to gain one pound every week or two for a couple of years. [Tr. 1153 (Roth)] Dr. Roth, for example, had one patient who gained 100 pounds in one year on olanzapine. [Tr. 1153 (Roth)] Aripiprazole, however, has substantially less risk of weight gain and associated metabolic disturbances compared to both typical and atypical antipsychotics. [Tr. 1152-53 (Roth); PTX 294] Although no antipsychotic drug is

perfect or cures schizophrenia, that fact does not detract from aripiprazole's clinical benefits over other antipsychotics. [Tr. 1163 (Roth)]

Aripiprazole has been approved for the treatment of schizophrenia in both adults and pediatric patients 10 to 17 years of age. [DTX 564] In addition, aripiprazole has been approved for several other indications, including as an add-on treatment for major depressive disorders, for acute treatment of adults with manic or mixed episodes associated with Bipolar I Disorder, for the acute treatment of pediatric patients 10 to 17 years of age with manic or mixed episodes associated with Bipolar I Disorder, for maintenance treatment of Bipolar I Disorder, for the acute treatment of agitation associated with schizophrenia or Bipolar I Disorder, and for the treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years of age. [DTX 564; Tr. 1360-61 (Roth); Tr. 2062 (Jarosz); PTX 372] Defendants introduced no evidence that aripiprazole's efficacy in treating those medical conditions would have been known or expected to a person of ordinary skill in 1988.

Dr. Roth's testimony concerning aripiprazole's unique pharmacologic and clinical properties was unchallenged at trial. Defendants did not dispute that no other FDA-approved antipsychotic besides aripiprazole is a partial agonist at dopamine receptors. [Tr. 1064 (Roth); PTX 372] Nor did Defendants dispute that since at least 1994, when the first promising clinical results of aripiprazole were publicly reported, scientists have attempted to make other drugs like aripiprazole. [Tr. 1062 (Roth)] To date, none of those research efforts to replicate aripiprazole's unique properties have succeeded. [Tr. 1062-1063 (Roth)] In fact, Defendants' experts essentially ignored aripiprazole's unique pharmacology in their testimony. Defendants presented no evidence that it would have been possible for a person of ordinary skill in the art in October 1988 to predict aripiprazole's unique pharmacologic properties based upon the teachings of the prior art.

H. Otsuka's Patenting of Aripiprazole and Related Compounds and the Prosecution of Otsuka's Patent Application Before the PTO

Otsuka sought patent protection for aripiprazole and certain related compounds by filing U.S. Patent Application No. 424,719 ("the '719 application") on October 20, 1989. The '719 application claimed priority from Japanese Application No. 63-276953, filed on October 31, 1988. [Pretrial Order Stipulated Facts ¶ 17]

During the prosecution of the '719 application before the PTO the Examiner cited U.S. Patent No. 4,824,840 ("the '840 patent"), a prior Otsuka patent. [DTX 116 at 0000065-71] The '840 patent is a division of U.S. Patent No. 4,734,416 ("the '416 patent"), another Otsuka patent, and therefore each of these patents has the same specification but includes different claims. [Tr. 479-80 (Goolkasian); DTX 121 at 00007-8] The specification of the '840 and '416 patents discloses a broad genus of carbostyril compounds that encompasses aripiprazole, although aripiprazole is not specifically disclosed. [DTX 121 at 00007-9; Tr. 1627-28 (Nichols)] The specification discloses about 500 specific carbostyril derivatives, including the "unsubstituted butoxy" compound relied upon by Defendants. [*Id.*] The PTO ultimately concluded that the patent claims are patentable over the prior art. [DTX 116 at 0000144-45]

The '528 patent was subsequently examined a second time by the PTO during a reexamination proceeding initiated by Otsuka. Otsuka filed a Request for *Ex Parte* Reexamination Proceedings on August 11, 2004. [DTX 121 at 00002-47] Otsuka's Reexamination Request cited to dozens of references, highlighting certain disclosures in those references and specifically identified various compounds disclosed in those references.

For example, Otsuka identified the unsubstituted butoxy compound several times in the Reexamination Request. Otsuka indicated that this compound was disclosed in multiple prior art references, including the '416 patent, German Patent No. 2,912,105 ("the DE '105 patent") and the Banno article. [DTX 121 at 00008, 00009 ("Example 54"), 00011 ("Example 54"), 00020 ("Example Vc-3")]. Otsuka further commented that this compound is a "non-halogenated analog of claim 12," the claim directed to aripiprazole, thus specifically identifying its structural similarity to aripiprazole. [DTX121 at 00008]

Otsuka also specifically identified in the Reexamination Request the compound 7-{3-[4-(2,3-dimethylphenyl)-1-piperazinyl]-propoxy}-carbostyril, which is sometimes referred to as OPC-4392. Otsuka pointed out where this compound was disclosed in multiple references including the DE '105 patent, the Banno article and various articles concerning this compound and its pharmacological properties. [DTX 121 at 00011 ("Example 313"), 00014 ("Compound 3"), 00020 ("Example VIc-4") and 00023-24]

Otsuka further specifically identified the 2,3-dichloro substituted propoxy compound in the Reexamination Request, noting its disclosure in the DE '105 patent and the Banno article. [DTX 121 at 00011 ("Example 317"), 00020 ("Example Vc-17")] Otsuka noted that an argument could be made that there is a "close structural similarity" between the 2,3-dichloro substituted propoxy compound and the claimed compounds, including that of claim 12, the claim directed to aripiprazole. [DTX 121 at 00012, 00020]

Otsuka stated in the Reexamination Request that it could be argued that the multiple cited documents raised a substantial new question of patentability. Otsuka additionally explained, with respect to the '416 patent, that "it can be argued that the use of the described compounds as

antischizophrenia agents is specifically contemplated." [DTX 121 at 00007] These statements were not admissions as to the teachings of the prior art or the possible unpatentability of the claims. Rather, Otsuka's discussion of the prior art demonstrates its good faith in these proceedings before the PTO, in which it attempted to identify the arguments that *might* be raised against the patentability of the claims. The entirety of the reexamination proceedings demonstrates that Otsuka consistently argued that the '416 patent did not teach that any particular compounds might be antipsychotics and that the patent claims were patentable over all of the prior art.

The PTO granted Otsuka's Reexamination Request on September 13, 2004 and issued an Office action on January 14, 2005, including various claim rejections based on the cited prior art. [DTX 121 at 01144-51 and 01235-48] The PTO cited to five exemplary compounds in support of its claim rejections based on the '416, '840 and DE '105 patents. These compounds included the unsubstituted butoxy compound, but did not include the 2,3-dichloro substituted propoxy compound or OPC-4392. Despite being made aware of OPC-4392 and the 2,3-dichloro substituted propoxy compound and their disclosures in these and other references cited in the Reexamination Request, the PTO did not cite to either of those compounds in this or any of its other claim rejections. [*Id.*] In response to the PTO's claim rejection based on the '416, '840 and DE '105 patents, Otsuka argued that:

> Fourth, while these references may suggest that their compounds may be useful for treating central nervous disorders, generally, there is no evidence that the five exemplary carbostyril compounds identified by the Examiner have such properties, let alone the recited property of treating schizophrenia. In fact, all of the testing is directed to very different properties, such as antihistamine, anaesthesia, and analgetic activities. *See* Exhibit C ['416 patent] at Col 31, line 1 to col. 36, line 10.

[DTX 121 at 01274] There is no dispute among the parties that the cited references did not contain any experimental evidence that any of the disclosed compounds had the property of treating schizophrenia. [Tr. at 129 (Press) ("there is no data in the '416 patent with respect to antipsychotic activity")] Accordingly, this argument by Otsuka was factually correct.

The PTO maintained its rejections in a second Office action. [DTX 121 at 01320-34] In its second Office action, the PTO again did not cite to either the 2,3-dichloro substituted propoxy compound or OPC-4392 in support of any of its claim rejections. These compounds were never mentioned in support of any claim rejections issued by the PTO during the reexamination proceedings.[1] [DTX 121 at 01320-34]

In response to the PTO's second Office action, Otsuka conducted an Interview with the PTO on September 13, 2005, and then filed a Request for Reconsideration on September 14, 2005. [DTX 121 at 01340-41 and 01342-1400] Along with its Request for Reconsideration, Otsuka submitted a declaration by Dr. Tsyoshi Hirose including test data for representative claimed compounds compared to structurally related prior art compounds. [DTX 121 at 01365-1400]

Otsuka and the PTO had reached agreement as to which were the closest prior art compounds to the compounds claimed in the '528 patent during the interview that took place on September 13, 2005, prior to the submission of the Hirose declaration on September 14, 2005. [DTX 0121 at 01341] Otsuka memorialized the substance of the interview in its Request for Reconsideration, reporting that

[1] Defendants repeatedly stated in their trial brief and their opening statement that during the reexamination proceedings the PTO rejected the patent claims over the 2,3-dichloro propoxy compound, and maintain this argument in one portion of their Post-Trial Findings. [Def. FOFCOL, page 15] These statements are factually incorrect as demonstrated by the reexamination record and conceded by Defendants in another portion of their Post-Trial Findings. [DTX 121; Def. FOFCOL, page 101]

the PTO had agreed with Otsuka that "the [Hirose] declaration provides a comparison of results between the claimed carbostyril compounds and the closest prior art, i.e, where the only structural distinction between the compared set of compounds is a butoxy, rather than a propoxy, bridging group, such as contained, for example, in the compound of Example 317 from DE '105, which is identical to Example Vc-17 in the Banno article." [DTX 121 at 01344]

The PTO thus ultimately concluded that the closest prior art compounds were those tested in the Hirose declaration. These compounds included the 2,3-dichloro propoxy compound but did not include either the unsubstituted butoxy compound or OPC-4392. [DTX 121 at 01368-69]

Following Otsuka's submission of its Request for Reconsideration and the accompanying Hirose declaration, the PTO issued a Notice of Intent to Issue *Ex Parte* Reexamination Certificate on October 27, 2005, indicating that the PTO had confirmed the patentability of claims 1-21 and deemed patentable claims 22-24, which had been newly presented in the reexamination. [DTX 121 at 01411-12] The Reasons for Patentability/Confirmation, which were signed by a group of three PTO examiners, stated that "[t]he compound claims 1-21 are found to be allowable since applicants have compared their compounds with the closest prior art. The ones with just one difference in the linker chain, propyloxy to a butoxy [chain], shows a clear unexpected result in the ED50 values." [DTX 121 at 01412]

The PTO issued a Reexamination Certificate for the '528 patent on June 13, 2006. [DTX 121 at 01426-28]

IV. FINDINGS OF FACT RELATING TO DEFENDANTS' ALLEGATIONS OF OBVIOUSNESS AND OBVIOUSNESS-TYPE DOUBLE PATENTING

Each of claims 12, 17, and 23 of the '528 patent recites, as a limitation, the compound aripiprazole described by its chemical name: 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril. [PTX 1] Claim 17 further specifies a pharmaceutical composition containing aripiprazole for the treatment of schizophrenia, and claim 23 specifies a method of treating schizophrenia by administering a pharmaceutical composition containing aripiprazole. [PTX 1] As depicted in the chemical drawing above, aripiprazole is a carbostyril derivative that includes, in a specific configuration, a 3,4-dihydrocarbostyril group, a butoxy linker, a piperazine ring, and a phenyl ring with chlorine substituents at the 2 and 3 positions of the phenyl ring. [Uncontested Fact, Pretrial Stip. at ¶¶ 24-27]

Defendants do not contend that aripiprazole is described in the prior art. [*See, e.g.*, Tr. 214 (Press)] Instead, using legally improper hindsight analysis, Defendants argue that a person of ordinary skill in October 1988 would have selected the unsubstituted butoxy compound, OPC-4392, or the 2,3-dichloro substituted propoxy compound as a starting or "lead" compound from among hundreds of other carbostyril derivatives described in the prior art, allegedly knowing that these compounds would have antipsychotic activity, then would have modified them to arrive at aripiprazole. These assertions are factually unsupported.

A. Level of Ordinary Skill in the Art

In forming his opinions, Dr. Roth analyzed the level of ordinary skill in the art of antipsychotic drug discovery in October 1988. [Tr. 1120-1121 (Roth)] He considered this Court's prior decision in *Janssen Pharmaceutica N.V. v. Mylan Pharmaceuticals, Inc.*, 456 F. Supp. 2d 644, 670 (D.N.J.

2006), *aff'd*, 233 Fed. Appx. 999 (Fed. Cir. 2007), in which the person of ordinary skill was defined as someone having a master's degree in chemistry, medicinal chemistry, or pharmacy, or a bachelor's degree in one of those fields with at least two years of experience in researching antipsychotic drugs. [Tr. 1121 (Roth)] Dr. Roth found that definition reasonable based on his own experience and personal knowledge of individuals actively engaged in antipsychotic drug discovery both in his lab and elsewhere. [Tr. 1121-1122 (Roth)] For example, the individual who serves as the head of the High Throughput Screening Center at UNC's Drug Discovery Institute has a bachelor's degree. The same person previously ran high throughput screening for Eli Lilly. [Tr. 1123 (Roth)]

In forming his opinions, Dr. Nichols similarly adopted and applied the definition of a person of ordinary skill in the art that was rendered in the *Janssen* case with respect to risperidone, which was a master's level of experience with some years of experience. [Tr. 1527-1529 (Nichols)]

Defendants contend that because antipsychotic drug discovery in the 1980s was conducted by teams of individuals, a person of ordinary skill in the art must have the attributes of that entire team. [Tr. 618-619 (Castagnoli)] Focusing on attributes of this team, Defendants failed to directly challenge Otsuka's testimony concerning the qualifications of an average worker engaged in this area of research. Moreover, while Defendants point to the qualifications of the inventors of the '528 patent, this is not dispositive, and the Court finds that the inventors here exhibited extraordinary skill in the art.

Neither of Otsuka's experts who opined on matters of obviousness considered the level of ordinary skill determinative in their evaluation of Defendants' obviousness allegations. Dr. Roth testified that his opinions would not change if the hypothetical person of ordinary skill in the art had a Ph.D. rather than a master's degree. [Tr. 1123 (Roth)] The number of years of experience of the

person of ordinary skill in the art also would not change his analysis. [Tr. 1123-1124 (Roth)] Nor would his opinions change if the hypothetical person of ordinary skill in the art comprised a "team" of Ph.D. scientists as Defendants propose. [Tr. 1124 (Roth)] Dr. Nichols likewise testified that his opinions would not change if the hypothetical person of ordinary skill in the art had a Ph.D. rather than a master's degree. [Tr. 1529 (Nichols)] Nor would his opinions change if the person of ordinary skill in the art had more years of experience or comprised a team of Ph.D. scientists. [Tr. 1529-1530 (Nichols)]

Accordingly, and for the reasons discussed in Section VI.A.2. below, the court finds that a person of ordinary skill in the art of antipsychotic drug discovery in October 1988 would be an individual having a master's degree in chemistry, medicinal chemistry, or pharmacy, or a bachelor's degree in one of those fields with at least two years of experience in researching antipsychotic drugs. The person of ordinary skill would not comprise a "team" of Ph.D. scientists as Defendants propose.

B. A Person of Ordinary Skill in the Art Would Have Chosen a Clozapine-like Compound as a Lead Compound

A person of ordinary skill in the art in October 1988 most likely would have started with a known antipsychotic such as clozapine if he or she wanted to create an improved antipsychotic drug. [Tr. 1591-92 (Nichols); Tr. 1169-1170 (Roth)] Clozapine was considered "the gold standard" antipsychotic drug with ideal properties except for its potential to cause agranulocytosis. [Tr. 1592 (Nichols)]

Prior to October 1988, researchers made many clozapine-like compounds as potential antipsychotics. [Tr. 1592 (Nichols); Tr. 1170 (Roth)] Schizophrenia researchers would have known of clozapine-like potential antipsychotics because research on clozapine analogs was described in the

scientific literature before October 1988. [Tr. 1171 (Roth)] Indeed, the development of clozapine-like potential antipsychotics remained a promising area of antipsychotic drug discovery well after 1988. [Tr. 1174-1178 (Roth); Tr. 1592 (Nichols); PTX 281; PTX 132]

Examples of clozapine-like potential antipsychotics that researchers have made include clotiapine, metiapine, amoxapine, perlapine, loxapine, fluperlapine, isoclozapine, des-chloroclozapine, flumezapine, tilozepine, doclothepin, octoclothepine, desmethylclozapine, olanzapine, oxyprothepine, zotepine, quetiapine, and asenapine as well as those clozapine analogs identified in PTX 118, PTX 124 and PTX 296. [Tr. 1596-97 (Nichols), Tr. 1171-72 (Roth); PTX 288; PTX 132; PTX 281; PTX 289; PTX 297; PTX 118; PTX 297; PTX 124; PTX 296; PTX 783; PTX 785] Most of these clozapine analogs were known to researchers prior to October 31, 1988, as illustrated in PTX 785. Dr. Nichols explained that these exemplary clozapine analogs represent a small percentage of the total number of clozapine analogs and "probably thousands of these compounds were made." [Tr. 1597 (Nichols)] Dr. Roth similarly confirmed that many clozapine analogs were made in the 1980s because this was an active area of scientific research. [Tr. 1172 (Roth)]

Loxapine is a clozapine-like typical antipsychotic drug that was approved prior to October 1988. [Tr. 1605 (Nichols)] Other clozapine-like compounds that subsequently became FDA-approved atypical antipsychotics include olanzapine (approved in 1996), quetiapine (approved in 1997), and asenapine (also known as ORG-5222; approved in 2009). [Tr. 1577-78, 1586-87, 1605 (Nichols); Tr. 1172 (Roth)] These compounds do not cause agranulocytosis like clozapine. [Tr. 1172 (Roth)] None of these clozapine-like antipsychotics are similar in structure to aripiprazole. [Tr. 1607-08 (Nichols)]

Defendants failed to rebut Otsuka's evidence that clozapine-like compounds would have been the most likely lead compounds in 1988 for purposes of antipsychotic drug discovery. To the contrary, when their expert Dr. Press was asked on cross-examination whether he agreed that clozapine was "a truly remarkable lead compound," he answered: "Yes, for several reasons." [Tr. 202 (Press)] Dr. Press also testified that clozapine was considered "a new profile of activity" in the 1970s and 1980s and that, after clozapine's agranulocytosis problem was discovered, researchers began looking for antipsychotics that "had the activity profile of clozapine." [Tr. 195-6 (Press)] When he was employed by Lederle Laboratories in the late 1970s and early 1980s, Dr. Press himself sought to develop potential antipsychotics that had an activity profile like clozapine. [Tr. 196-197 (Press)] Indeed, the potential antipsychotics his group worked on "were modeled after clozapine." [Tr. 198-200 (Press); PTX 704; PTX 114; PTX 296] There is no evidence that Dr. Press ever worked on any potential antipsychotics other than those modeled after clozapine.

In a prior patent litigation involving the antipsychotic drug olanzapine, Dr. Press stated in an affidavit that finding an improved clozapine was the subject of everyone's research. [Tr. 201 (Press)] In the present litigation, however, Dr. Press inexplicably failed to even discuss in his expert reports efforts by researchers to develop clozapine analogs in October 1988. [Tr. 203 (Press)] He provided no such testimony at trial.

Defendants' other medicinal chemistry expert, Dr. Castagnoli, confirmed at trial that he conceded during his deposition he did not have a sufficient understanding of the attractive features of clozapine to determine whether it would have been a possible lead compound that a person of ordinary skill in the art might have pursued in October 1988. [Tr. 824-27 (Castagnoli)]

Defendants introduced no evidence at trial that a person of ordinary skill in the art in October 1988 would have selected any carbostyril derivative (including OPC-4392, the unsubstituted butoxy compound, or the 2,3-dichloro-substituted compound) as a lead compound for antipsychotic drug discovery over a clozapine-like compound.

Clozapine-like compounds would not have led a person of ordinary skill in the art to aripiprazole because, as Dr. Nichols testified, clozapine and aripiprazole are not structurally similar. [Tr. 1604 (Nichols)] There is no contrary evidence in the record.

C. A Person of Ordinary Skill in the Art Alternatively Would Have Chosen a Risperidone-like Compound as a Lead Compound

Other than clozapine-like compounds, a person of ordinary skill in the art in October 1988 likely would have selected a risperidone-like compound as a lead compound for development as a potential antipsychotic. [Tr. 1608 (Nichols); Tr. 1178-1179 (Roth)] Risperidone was publicly known before October 1988 as a promising potential atypical antipsychotic drug. [Tr. 1186 (Roth); PTX 305; DTX 990] For example, a published abstract reported that, in the first multicenter open dose finding trial of 120 therapy-resistant chronic psychotic patients, it had been demonstrated that risperidone combined a very efficient antipsychotic effect with a significant improvement of negative and dystonic symptoms without inducing acute EPS. [Tr. 1181 (Roth); DTX 990] The abstract also described a follow-up study designed to evaluate the therapeutic effect and safety of higher doses of risperidone in psychotic patients. [Tr. 1181-82 (Roth); DTX 990] Doses up to 20 milligrams of risperidone daily significantly improved both positive and negative symptoms of schizophrenia with no increase of EPS and no clinically relevant effects on cardiovascular or electrocardiogram parameters. [Tr. 1181-82 (Roth); DTX 990] Thus, risperidone appeared to be safe and well tolerated

in schizophrenia patients and to exhibit excellent antipsychotic activity. [Tr. 1180-1182 (Roth); DTX 990]

A second abstract in the same publication similarly reported that it had been demonstrated that risperidone at a mean daily dose of 5 milligrams combined a very efficient antipsychotic effect with a significant improvement of negative and dystonic symptoms without inducing acute EPS. [Tr. 1182 (Roth); DTX 990] In addition, existing EPS were reduced even though anti-Parkinsonian medication was stopped. [Tr. 1182 (Roth); DTX 990]

A person of ordinary skill in the art in October 1988 seeking to develop an improved antipsychotic drug would have been interested in these abstracts reporting risperidone's successful clinical trials. [Tr. 1608-10 (Nichols)] As Dr. Roth testified, these "were very exciting results" in part because Janssen's work "carries a lot of weight in the psychiatric community." [Tr. 1182-1183 (Roth)] The results showed that risperidone had antipsychotic activity without EPS, which was "what we [schizophrenia researchers] were looking for," making it "a huge, huge finding and very exciting at the time." [Tr. 1182-1183 (Roth)] Defendants never attempted to rebut Dr. Roth's testimony concerning the significance of these successful clinical results for risperidone, which were published prior to October 1988. In fact, Dr. Press testified on cross-examination that "risperidone was at a stage of development [by October 1988] where it was in the clinic and was showing good effect." [Tr. 209 (Press)]

Risperidone was approved as an atypical antipsychotic drug in the United States in 1993. [Tr. 1586, 1610 (Nichols); Tr. 1183 (Roth)] Other risperidone-like compounds that subsequently gained FDA approval as atypical antipsychotics include ziprasidone (developed by Pfizer and approved in 2001), paliperidone (developed by Janssen and approved in 2006), and iloperidone (developed by

Vanda and approved in 2009). [Tr. 1587, 1612-13 (Nichols)] Another risperidone-like compound, lurasidone (developed by Dainippon Sumitomo), succeeded in clinical trials and is pending final approval at the FDA. [Tr. 1586-87 (Nichols); Tr. 1184 (Roth)] Each of these compounds mimics in some respects the structural features and pharmacological properties of risperidone. [Tr. 1587, 1612-1613 (Nichols); Tr. 1183-1184 (Roth)] None of the risperidone-like antipsychotics are similar in structure to aripiprazole. [Tr. 1611, 1613 (Nichols)]

Dr. Castagnoli confirmed at trial that he lacked a sufficient understanding of the attractive features of risperidone to determine whether it would have been a possible lead compound that a person of ordinary skill in the art might have pursued in October 1988. [Tr. 826-27 (Castagnoli)]

Defendants introduced no evidence at trial that a person of ordinary skill in the art in October 1988 would have selected any carbostyril derivative (including OPC-4392, the unsubstituted butoxy compound, or the 2,3-dichloro substituted propoxy compound) as a lead compound for antipsychotic drug discovery over a risperidone-like compound.

Risperidone-like compounds would not have led a person of ordinary skill in the art to aripiprazole because, as Dr. Nichols testified, risperidone and aripiprazole are not structurally similar. [Tr. 1611, 1613 (Nichols)] There is no contrary evidence in the record.

The atypical antipsychotic drugs that have been approved in the United States to date fall into three general classes: (1) clozapine-like atypical antipsychotics (clozapine, olanzapine, quetiapine, and asenapine); (2) risperidone-like atypical antipsychotics (risperidone, ziprasidone, paliperidone and iloperidone); and (3) aripiprazole, which is unique. [Tr. 1185-1186 (Roth)] Other than aripiprazole, no atypical antipsychotic has been approved in the United States to date that is structurally unrelated to clozapine or risperidone. [Tr. 1614 (Nichols)] Clozapine and risperidone

were therefore the basis for all currently approved atypical antipsychotics in the United States except aripiprazole. [Tr. 1614 (Nichols)] This undisputed evidence concerning groups of related atypical antipsychotics supports the Court's finding that by far the most likely lead compound or compounds for antipsychotic drug research in October 1988 would have been a clozapine-like or risperidone-like compound.

D. A Person of Ordinary Skill Would Not Have Chosen Any Carbostyril Derivative as a Lead Compound

1. OPC-4392 Failed to Treat Positive Symptoms and Had Serious Side Effects

A person of ordinary skill in October 1988 would not have selected any carbostyril derivative as a lead compound for development as a potential antipsychotic because no carbostyril derivative had ever been shown by 1988 to adequately treat schizophrenia. To the contrary, the only carbostyril derivative that had even been tested in humans as a potential antipsychotic, OPC-4392, failed because it did not effectively treat the positive symptoms of schizophrenia and had serious side effects.

a. Gerbaldo (March 1988)

The failure of OPC-4392 was made evident in open label clinical studies described in a March 1988 abstract authored by H. Gerbaldo et al., entitled "Treatment of Negative Symptoms of Schizophrenic Patients with the Partial Dopamine Agonistic Compound OPC-4392," published in *Psychopharmacology* ("the Gerbaldo abstract"). [DTX 990] The Gerbaldo abstract reported that, in a first open study of OPC-4392 in schizophrenia patients, "the most evident observation was an improvement in blunted affect [a negative symptom]." [Tr. 1201 (Roth); DTX 990] The abstract's conclusion similarly stated that OPC-4392 affected negative symptoms in patients with schizophrenia. [Tr. 1202 (Roth); DTX 990] Critically, however, the Gerbaldo abstract did not indicate that OPC-

4392 treated the positive symptoms of schizophrenia. [Tr. 1205 (Roth)] Dr. Roth therefore reasonably interpreted the abstract as suggesting that OPC-4392 had no effect on the positive symptoms of schizophrenia. [Tr. 1203 (Roth)] The Court accepts Dr. Roth's interpretation, which is consistent with the content of the abstract, including its title and conclusion, which refer only to negative symptoms. [DTX 990] Defendants offered no contrary interpretation of the Gerbaldo abstract in their proposed findings, essentially conceding that Dr. Roth's interpretation that OPC-4392 did not treat positive symptoms was correct. [*See also* Tr. 803 (Castagnoli) ("[W]hat 4392 lacked was this antipsychotic component.")]

The Gerbaldo abstract would not have encouraged a person of ordinary skill in the art in October 1988 to pursue OPC-4392 or other carbostyril derivatives as potential antipsychotics. [Tr. 1203 (Roth)] As Dr. Roth explained, "since an antipsychotic drug ... by definition has to treat the positive symptoms of schizophrenia, one would have not been encouraged by this particular abstract." [Tr. 1203 (Roth)]

With respect to the Gerbaldo abstract's report that OPC-4392 improved negative symptoms, Dr. Roth explained: "One skilled in the art would be very unimpressed with this statement, knowing, in fact, that drugs that are ineffective in treating schizophrenia frequently in these sorts of trials will show some transient effect on negative symptoms." [Tr. 1409-1410 (Roth)] Defendants introduced no relevant evidence to the contrary as none of their experts were qualified to testify about clinical aspects of antipsychotic medications. [Tr. 829-830 (Castagnoli); Tr. 721-23 (Marshall); Tr. 281 (Press)] Further, even if OPC-4392 did improve negative symptoms, it would not have been considered an antipsychotic drug because it did not treat the positive symptoms of schizophrenia. [Tr. 1042-1043 (Roth)]

The Gerbaldo abstract concerning OPC-4392 is found on the same page as the two abstracts discussed above relating to risperidone. [Tr. 1203 (Roth); DTX 990] Based on the information in these three abstracts, risperidone would have appeared more promising to a person of ordinary skill in the art in October 1988 as a lead compound for antipsychotic drug discovery. [Tr. 1205 (Roth)] Risperidone was reported to improve both positive and negative symptoms of schizophrenia, which were "highly positive results." [Tr. 1203-1204 (Roth); *see also* Tr. 209 (Press) ("I believe that risperidone was at a stage of development [by October 1988] where it was in the clinic and was showing good effect."); DTX 990] By contrast, nothing in the Gerbaldo abstract indicated that OPC-4392 had antipsychotic activity. [Tr. 1205 (Roth)] According to Dr. Roth, the contrast between the risperidone and OPC-4392 clinical results was striking. [Tr. 1203-1204 (Roth); DTX 990]

b. Murasaki (1987)

Essentially disregarding the Gerbaldo abstract, Defendants assert that a person of ordinary skill in October 1988 would have been interested in pursuing carbostyril derivatives as potential antipsychotics based on a brief discussion of OPC-4392 in a 1987 publication by Mitsukuni Murasaki in the *Japanese Journal of Clinical Psychiatry* ("the 1987 Murasaki paper"). [DTX 388T] The 1987 Murasaki paper, however, actually supports Otsuka's position that a person of ordinary skill would not have been interested in OPC-4392 or other carbostyril derivatives as potential antipsychotics.

The *Japanese Journal of Clinical Psychiatry* is not a well-known journal in the field of antipsychotic drug discovery. [Tr. 1193 (Roth)] Dr. Roth, for example, had "never heard of it before [he] was asked to be an expert for this case." [Tr. 1193 (Roth)] Defendants introduced no evidence that this journal would have been given any significant consideration by persons skilled in the art of antipsychotic drug discovery in October 1988.

OPC-4392 was discussed at page 1517 of the translation of the 1987 Murasaki paper. [Tr. 1193 (Roth); DTX 388T] The first sentence of the second paragraph reported: "In the results of the Phase II trials, the antipsychotic action was not strong, but the strength of the activating action stood out." [Tr. 1193-1194 (Roth); DTX 388T] Dr. Roth reasonably interpreted that sentence to mean that OPC-4392 had "no antipsychotic activity." [Tr. 1194 (Roth)] The Court accepts Dr. Roth's interpretation based on his extensive clinical experience.

Dr. Press stated incorrectly at least nine times in his initial expert report that OPC-4392 had "strong" antischizophrenic activity. [Tr. 273 (Press)] He admitted at trial that, when he made those incorrect statements, he had not even considered the 1987 Murasaki paper. [Tr. 279-280 (Press)]

The statement in the 1987 Murasaki paper that the "strength of the activating action stood out" would have been "a red flag" for people who treat schizophrenia. [Tr. 1194 (Roth); DTX 388T] As Dr. Roth explained, "[o]ne of the worst things you can have on a floor where people with schizophrenia are is to have them activated." [Tr. 1194 (Roth)] Antipsychotic drugs tend to diminish the overall state of activation of patients. [Tr. 1194-1195 (Roth)] Schizophrenia patients may become activated, however, when they have been given an ineffective medication. When persons with schizophrenia become activated, they are more likely to act out on their delusions and hallucinations. [Tr. 1195 (Roth)] For example, activated schizophrenia patients may experience "command hallucinations" that cause them to attack other people. [Tr. 1195 (Roth)] Activation of schizophrenia patients can therefore be quite dangerous, particularly in an acute clinical setting. [Tr. 1195 (Roth)]

Schizophrenia patients who become activated often talk in a loud voice and may become belligerent. [Tr. 1358 (Roth)] Dr. Roth explained, for example, that activated patients often would

come to his attention from nurses who feared for their safety or other patients' safety. [Tr. 1358-1359 (Roth)]

Defendants did not rebut Dr. Roth's testimony that Murasaki's report that OPC-4392 activated schizophrenia patients would have been viewed as a "a red flag." [Tr. 1194 (Roth); DTX 388T] Indeed, Dr. Press admitted that he did not know whether activating action would be desirable or undesirable in an antipsychotic drug. [Tr. 284 (Press)] Similarly, when asked, "[W]hat is your understanding of that term 'the activating action stood out'; what does that mean?" he answered, "I do not know the answer to that." [Tr. 285 (Press)]

The 1987 Murasaki paper reported some improvement in negative symptoms and speculated that OPC-4392 might be useful for the treatment of the chronic stage of schizophrenia. [Tr. 1194 (Roth); DTX 388T] As Dr. Roth explained, however, "even if you take a person off an antipsychotic drug and put them on placebo, you will see improvement in negative symptoms" because antipsychotic drugs "in general worsen the negative symptoms." [Tr. 1195 (Roth)] It is therefore not uncommon for negative symptoms to improve in clinical trials when schizophrenia patients are on placebo or inactive medication. [Tr. 1198-1199 (Roth)] Defendants introduced no evidence to the contrary; thus, Murasaki's report on improved negative symptoms does not establish that a person of ordinary skill in the art would have been interested in pursuing OPC-4392 or other carbostyril derivatives as potential antipsychotics.

Defendants contend that Murasaki reported that OPC-4392 had a good side-effect profile with respect to EPS, prolactin levels, and orthostatic hypotension. [Def. FOFCOL, page 28] Murasaki, however, makes no reference to orthostatic hypotension, and Defendants presented no evidence at trial to the contrary. As for Murasaki's report concerning EPS and prolactin levels, the absence of

these side effects was consistent with the fact that OPC-4392 was also reported as having no antipsychotic activity. Dr. Press confirmed, for example, that neither a placebo (sugar pill) or diazepam (not an antipsychotic) would cause EPS. [Tr. 282 (Press)] Thus, as Dr. Roth testified, a person of ordinary skill would look at this paper, conclude that OPC-4392 did not work as an antipsychotic, and move on. [Tr. 1200 (Roth)]

In addition, the fact that OPC-4392 made it to Phase II clinical studies would not have been remarkable to a person of ordinary skill in the art in 1988 because many compounds make it to Phase II studies yet fail to become approved drugs. [Tr. 1200-1201 (Roth)]

For all these reasons, the 1987 Murasaki publication would not have encouraged a person of ordinary skill in the art to pursue OPC-4392 or other carbostyril derivatives as potential antipsychotics. [Tr. 1199-1200 (Roth)] If anything, the publication would have caused them to avoid OPC-4392 or similar compounds. [Tr. 1205-1206 (Roth)]

c. Murasaki (September 1988)

In addition to its lack of efficacy, OPC-4392 was reported to cause potentially serious side effects in a Phase I clinical study published in *Progress in Neuropsychopharmacology and Biological Psychiatry*. [Tr. 1189 (Roth); PTX 545] A copy of the publication was received by the University of California-San Diego library on September 12, 1988. This study indicated that OPC-4392 would not be safe at therapeutic doses. [PTX 545]

In the study, healthy males were given various doses of OPC-4392 to determine the maximum tolerated dose of the drug and to examine its adverse effects. [Tr. 1189 (Roth)] The paper also reported pharmacokinetic data and endocrine data. [Tr. 1189 (Roth)] It was a small study in seven male volunteers. [Tr. 1190 (Roth)]

The results were reported beginning on page 795 of the publication. In the section entitled "Clinical Pharmacology Symptoms," the paper reported that the "main clinical symptoms of OPC-4392 were sleepiness, weakness, fatigability, stagger, heavy headedness, disturbed concentration, nausea, etc." [Tr. 1190 (Roth); PTX 545] Thus, as Dr. Roth explained, OPC-4392 caused a number of neuropsychiatric side effects, including weakness, fatigability, staggering, and disturbed concentration, which would have been "a red flag in moving a compound forward for treating a psychiatric disease." [Tr. 1190 (Roth)] These side effects would have been "disturbing" to Dr. Roth in a Phase I clinical trial. [Tr. 1190 (Roth)]

In the "Clinical Pharmacology" section beginning on page 798, the paper reported that a 5 milligram dose of OPC-4392 caused side effects in normal humans that "were so severe that they were not able to perform daily routine work." [Tr. 1190-91 (Roth); PTX 545] Five milligrams is "a very low dose of a potential antipsychotic drug." [Tr. 1191 (Roth)] In pharmacokinetic studies, the healthy volunteers experienced a "disturbance of concentration and a difficulty in performing daily routine work" at 7 to 10 nanograms per milliliter of OPC-4392, which is a low drug level. [Tr. 1191 (Roth)] At 10 to 15 nanograms per milliliter of OPC-4392, the volunteers experienced "mental anguish to perform daily routine work." [Tr. 1191 (Roth)] This "mental anguish" clinical finding for OPC-4392 "would have been a huge red flag" to the FDA. [Tr. 1191 (Roth)] As Dr. Roth explained, "in treating schizophrenia we're trying to diminish mental anguish, not to induce it." [Tr. 1191 (Roth)]

Most researchers would have viewed OPC-4392 as "a failed compound based on the Phase I data." [Tr. 1191-1192 (Roth)] The Phase I results for OPC-4392 therefore would not have encouraged a person of ordinary skill in the art in 1988 to pursue OPC-4392 or other carbostyril

derivatives as potential antipsychotics. [Tr. 1192 (Roth)] Rather, the results would have further led a person of ordinary skill in the art away from OPC-4392 or similar compounds.

2. Studies of OPC-4392 in Rodents Would Have Been Irrelevant in View of the Unsuccessful Clinical Studies in Humans

Ignoring OPC-4392's inability to treat the positive symptoms of schizophrenia and side effects in humans, Defendants seek to rely on certain preclinical papers showing OPC-4392's effects in rodents. The rodent studies, however, would have been essentially irrelevant in October 1988 because by then the unsuccessful clinical results *in humans* had already been published for OPC-4392. [PTX 545; DTX 990] A person of ordinary skill in the art in October 1988 would have been more interested in clinical studies of OPC-4392 in humans rather than preclinical studies in rodents. [Tr. 1187 (Roth)] Defendants themselves acknowledge that "human trials trump animal studies." [Def. FOFCOL, page 113]

The preclinical rodent studies simply confirm that, before OPC-4392 failed in humans, Otsuka believed that OPC-4392 was a potential antipsychotic drug. [Tr. 1187 (Roth)] These papers, however, provide no scientific basis for a person of ordinary skill in the art in October 1988 to conclude that OPC-4392 or any other carbostyril derivative would be a therapeutically effective antipsychotic drug. [Tr. 1205 (Roth)]

Defendants' antipsychotic drug discovery expert, Dr. Press, did not investigate carbostyril derivatives while working at Lederle in the late 1970s and early 1980s. [Tr. 212 (Press)] Further, although he was supervising several groups of chemists in 1988, none of those groups pursued carbostyril derivatives as potential antipsychotics. [Tr. 194 (Press)] Dr. Press has, in fact, never performed any scientific research related to carbostyril derivatives. [Tr. 212 (Press)] In his testimony

in the olanzapine patent litigation, Dr. Press never identified carbostyril derivatives as suitable lead compounds for antipsychotic drug discovery. [Tr. 212 (Press)]

In sum, based on the published information available by October 31, 1988, a person of ordinary skill in the art would not have chosen OPC-4392 or any other carbostyril derivative as a lead compound for antipsychotic drug discovery. [Tr. 1205-1206 (Roth)] A person of ordinary skill certainly would not have selected any carbostyril derivative over a clozapine-like or risperidone-like compound.

3. Post-1988 Publications Confirm OPC-4392's Clinical Failure

During trial and in their post-trial submission, Defendants attempted to rely on papers published after the October 31, 1988, priority date to establish that OPC-4392 allegedly was a promising antipsychotic drug. Apart from the fact that these non-prior art publications would not have been available to the person of ordinary skill in the art in October 1988, they do not support Defendants' position. Indeed, they simply confirm that OPC-4392 failed as a potential antipsychotic.

A 2006 paper published by Murasaki in the *Japanese Journal of Clinical Psychopharmacology* reported that, during the clinical studies of OPC-4392 in the 1980s, some schizophrenia patients experienced "unfavorable increases in their levels of activity. The drug induced impulsive acts and violent behaviors in some cases and elicited and aggravated the positive symptoms, such as hallucination[s] and delusion[s] (as opposed to alleviating them)." [DTX 362T; Tr. 1412-1416 (Roth)] This description is fully consistent with Dr. Roth's testimony that OPC-4392 did not treat positive symptoms and activated schizophrenia patients in a potentially dangerous manner. [Tr. 1194-1195 (Roth)]

Dr. Roth's interpretation was further confirmed in an open label study of OPC-4392 published by Gerbaldo in November 1988. [DTX 394] Four of 11 patients discontinued the study before the two-week period, which was a high discontinuation rate. [Tr. 1423 (Roth); DTX 394] Two patients discontinued the study because of clinical deterioration: one due to aggressiveness and mutism (inability to speak) and another due to catatonic stupor. [Tr. 1423 (Roth); DTX 394] A third patient was excluded due to a suicide attempt, and a fourth was excluded due to death wishes. [Tr. 1425 (Roth); DTX 394]

These results indicated that OPC-4392 was ineffective in treating schizophrenia. [Tr. 1423 (Roth)] Catatonic stupor, for example, is the most extreme form of deterioration that one sees in schizophrenia. [Tr. 1423 (Roth)] Patients experiencing catatonic stupor maintain a fixed body posture and are completely unresponsive to all sensory modalities, including pain. [Tr. 1424 (Roth)] Moreover, that two of 11 patients were excluded because of a frank suicide attempt or suicidal ideations was "an extremely high instance" of very serious adverse events. [Tr. 1425 (Roth)] Dr. Roth testified that the level of adverse events for OPC-4392 reported in this paper was "unprecedented in [his] experience with treating people with schizophrenia." [Tr. 1426 (Roth)] He was struck by "the extreme worsening of psychopathology and suicidology that occurred with some of these patients" treated with OPC-4392, particularly given that there were only 11 patients in this study. [Tr. 1426 (Roth)]

If data such as those presented in this paper were presented to the FDA as part of a request for approval of an antipsychotic drug, OPC-4392 would not have advanced past Phase II. [Tr. 1426 (Roth)] Dr. Roth, for example, is aware of "instances in which clinical trials were stopped because of a suicide attempt with a patient in treating schizophrenia." [Tr. 1427 (Roth)]

Consistent with these post-1988 publications, OPC-4392 never became an approved antipsychotic drug. [Tr. 1205 (Roth); Tr. 286 (Press)]

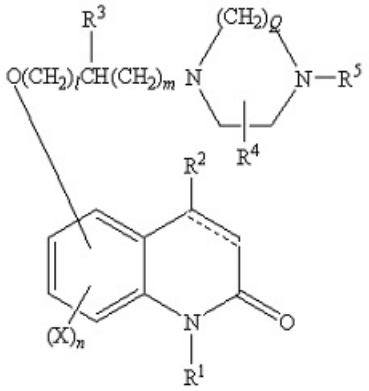
E. A Person of Ordinary Skill Would Not Have Selected the Unsubstituted Butoxy Compound as a Lead Compound

Even if a person of ordinary skill in 1988 would have been interested in carbostyril derivatives as potential antipsychotics, nothing in the prior art points to the unsubstituted butoxy compound as a promising lead compound. To the contrary, the prior art teaches away from it.

1. The '416 Patent Teaches Away from the Unsubstituted Butoxy Compound

Defendants rely primarily on the '416 patent, entitled "Pharmaceutically Useful Carbostyril Derivatives." [DTX 6] The PTO confirmed the patentability of the claims of the '528 patent over the '416 patent during the reexamination proceeding. [PTX 1 (Reexamination Certificate)] In addition, during both the original prosecution and reexamination of the '528 patent, the PTO found the claims patentable over a related patent (U.S. Patent No. 4,824,840) that discloses the same carbostyril derivatives as the '416 patent. [PTX 1 (Reexamination Certificate)]. Defendants' reliance on prior art that was already fully considered by the PTO highlights the weakness of their arguments.

The '416 patent describes an enormously broad group of carbostyril derivatives represented by the formula (1) shown below:



Formula (1) allows broad variation in the substituents R^1, R^2, R^3, R^4, R^5, and X, in the numbers *l* and *m* of methylene units (CH_2) in the alkoxy linker, in the number *n* of substituents X, in the positions of attachment of the alkoxy linker and the $(X)_n$ substituents on the bicyclic carbostyril or 3,4-dihydrocarbostyril ring system, and in the size *Q* and position of substitution by R^4 of the saturated ring containing two nitrogen atoms. [Tr. 1617-24 (Nichols)] In view of these potential structural variations, Formula (1) encompasses at least about 9 trillion different chemical structures. [Tr. 1617-24 (Nichols)]

The '416 patent does not describe the specific chemical formula of aripiprazole. [Tr. 1207 (Roth); Tr. 221 (Press); DTX 6]

At column 2, the '416 patent indicates that "the antihistaminic agents according to the present invention are effective as treating agents and prophylactic agents for various allergic diseases and symptoms ...." [DTX 6] The '416 patent also describes pharmacological test data consistent with an emphasis on antihistaminic activity, beginning with an "Antihistamine activity test" at column 31. [Tr. 1207-1209 (Roth)] As Dr. Roth explained, this is a test for antihistamines, not potential

antipsychotics. [Tr. 1209 (Roth)] He also pointed out that, based on the data presented, some of the compounds tested in the '416 patent were "extraordinarily potent antihistamines." [Tr. 1209 (Roth)]

At column 33, the '416 patent describes an anesthesia and sleep-increasing activity test. [Tr. 1209 (Roth); DTX 6] Because centrally active antihistamines cause sedation, antihistamines are commonly used as preanesthetic agents. [Tr. 1210 (Roth)] One way to test a preanesthetic agent is to examine its halothane anesthesia increasing activity, which measures a compound's central antihistamine activity. [Tr. 1210] This test is not one for potential antipsychotic activity. [Tr. 1210 (Roth)]

At column 34, the '416 patent describes a test for "Activity for inhibiting fighting behavior of mouse isolated singly for a long period of time," which seeks to identify compounds that have anti-serenic (anti-aggression) activity. It is not a test for potential antipsychotic activity. [Tr. 1210-1211 (Roth); DTX 6] At column 35, the '416 patent describes a test for analgetic activity, which measures peripheral antinociceptive (anti-pain or analgesic) activity, not potential antipsychotic activity. [Tr. 1211-1212 (Roth)] Also at column 35, the '416 patent describes an acute toxicity test, which measures a compound's safety, not potential antipsychotic activity. [Tr. 1213-1214 (Roth)]

There are no other pharmacological data in the '416 patent. [Tr. 1214 (Roth)] Thus, none of the pharmacological tests in the '416 patent relate to potential antipsychotic activity. [Tr. 1208 (Roth); Tr. 129, 225 (Press)] Because the '416 patent describes "extraordinarily potent" antihistamines, and the disclosed pharmacological tests are consistent with antihistamine activity, a person of ordinary skill in the art in October 1988 would have interpreted the '416 patent to be directed to antihistamines. [Tr. 1214 (Roth)] Dr. Roth himself concluded from reading the '416 patent that it is directed to antihistamines. [Tr. 1207-1208, 1214 (Roth)]

At columns 2 and 3, the '416 patent mentions the possible use of the compounds of the invention as "central nervous controlling agents." [Tr. 1214 (Roth); DTX 6] At column 3, lines 13-19, for example, the '416 patent suggests the compounds may be useful as "central nervous controlling agents such as central muscle relaxing agents, sleep-inducing agents, pre-operative drugs, antischizophrenia agents, sedatives, antianxiety drugs, anti-manic depressive psychosis agents, antipyretic agents, analgetic agents and depressors." [Tr. 1219 (Roth); DTX 6] Dr. Roth aptly described this sentence as a "miscellaneous laundry list of potential central nervous system indications." [Tr. 1219 (Roth)] A person of ordinary skill in the art in October 1988 would not have interpreted this sentence to mean that every compound disclosed in the '416 patent likely would have all ten of those listed potential therapeutic indications. [Tr. 1219-1220 (Roth)] No drug has been approved by the FDA for all ten of those potential indications. [Tr. 223-224 (Press)]

Nor would a person of ordinary skill in the art have expected that all of the compounds disclosed in the '416 patent would be antipsychotics. [Tr. 1219-1220 (Roth)] Indeed, it is undisputed there is no information in the '416 patent that would have allowed a person of ordinary skill in the art in October 1988 to determine which carbostyril derivatives, if any, are antipsychotics. [Tr. 1220 (Roth); Tr. 228-229 (Press)]

At column 3, lines 5-6, the '416 patent mentions without explanation "apomorphine vomiting inhibitory action," which is a test for antiemetic compounds that inhibit vomiting. It is not a specific test for antipsychotic activity. [Tr. 1214-1215 (Roth); DTX 6] In the same paragraph, the '416 patent also mentions without explanation "spontaneous movement controlling action," "hypermotion controlling action of rats," and "anti-methanphetamine [sic] action," none of which is a specific test for antipsychotic activity. [Tr. 1215-1218 (Roth)] Methamphetamine, for example, does many

things; it causes locomotion, elevates blood pressure, and elevates temperature. [Tr. 1217 (Roth)] None of these tests would be considered a screening method for evaluating potential antipsychotic activity. [Tr. 1220 (Roth)] Further, Defendants have no evidence that any of the compounds of the '416 patent were actually tested in any of these tests. [Tr. 226-228 (Press)]

Even if a person of ordinary skill in the art in October 1988 had looked to the '416 patent to select a lead compound for antipsychotic drug discovery, such person would not have selected the unsubstituted butoxy compound. [Tr. 1629 (Nichols); DTX 6] Beginning at column 4, line 47, the '416 patent lists many representative carbostyril compounds, and that list continues for several pages until column 13, line 47. [Tr. 1626 (Nichols)] The list identifies by name about 250 specific carbostyril derivatives (none of which is aripiprazole) and indicates that each of those compounds may exist in two forms, resulting in a total of about 500 specifically named carbostyril derivatives. [Tr. 1626-1628 (Nichols)] There is substantial variation in chemical structure among those 500 representative compounds consistent with the broad genus of Formula (1). [Tr. 1628 (Nichols)]

One of those 500 carbostyril derivatives is the unsubstituted butoxy compound, which is identified at column 6, lines 41 to 42 by its chemical name ("7-[4-(4-Phenylpiperazinyl)butoxy]-3,4-dihydrocarbostyril"). [Tr. 1628-1629 (Nichols)] The term "unsubstituted butoxy compound," which Defendants coined, does not actually appear in the '416 patent. [Tr. 235 (Press)]

No preferences are stated among the 500 compounds listed in the '416 patent, and no information is provided that could have led a person of ordinary skill to pick out a compound that would be the most potent or have the least side effects. [Tr. 234 (Press)] Moreover, nothing in the list of 500 representative compounds in any way highlights or points to the unsubstituted butoxy compound. [Tr. 1629 (Nichols); Tr. 236 (Press)] If a person of ordinary skill in the art in October

1988 were relying on the '416 patent to select a lead compound for antipsychotic drug discovery, there is no reason that person would have selected the unsubstituted butoxy compound over one of the 500 or so other representative compounds listed in the '416 patent. [Tr. 1629 (Nichols)]

In addition, it is undisputed that the claims of the '416 patent specifically describe the unsubstituted butoxy compound as an antihistaminic agent. Claim 116 of the '416 patent identifies the unsubstituted butoxy compound; it is the fourth compound listed in that claim. [Tr. 1222-1223 (Roth); Tr. 1630 (Nichols); Tr. 240 (Press)] Claim 116 refers back to claim 50, which is a method for producing an antihistaminic effect in a mammal. [Tr. 1223 (Roth); Tr. 1630 (Nichols); Tr. 241 (Press)] In view of claims 116 and 50 when read together, a person of ordinary skill in the art in October 1988 would have concluded that the unsubstituted butoxy compound is an antihistamine. [Tr. 1222-1224 (Roth); Tr. 1631 (Nichols); Tr. 240-241 (Press)]

None of the 118 claims of the '416 patent describe the unsubstituted butoxy compound as an antipsychotic. [Tr. 238 (Press)] Claims 25-29, for example, are directed to a central nervous controlling effect rather than an antihistaminic effect. [Tr. 1632 (Nichols)] Those claims, however, exclude the unsubstituted butoxy compound from their scope because they are limited to 6-position isomers with a propoxy linker whereas the unsubstituted butoxy compound is a 7-position isomer with a butoxy linker. [Tr. 1632-1634 (Nichols); Tr. 243-245 (Press)]

A person of ordinary skill in the art in October 1988 would not have selected an antihistamine such as the unsubstituted butoxy compound as a lead compound for antipsychotic drug discovery. [Tr. 1631, 1634 (Nichols); Tr. 1386-1389 (Roth)] Instead, they would have selected as a lead compound some molecule that had antipsychotic activity in an animal or a preclinical model. [Tr. 1632 (Nichols)]

If one correlates the average clinical daily dose of antipsychotic drugs with dopamine receptor affinity, there is an exceedingly high correlation. [Tr. 1386 (Roth); PTX 768] On the other hand, there is "absolutely no correlation" between the average clinical daily dose of antipsychotic drugs and histamine receptor affinity. [Tr. 1386 (Roth); PTX 768] Clinical potency is therefore clearly related to dopamine receptor affinity, but not related at all to affinity at histamine receptors. [Tr. 1387 (Roth)] As Dr. Roth explained, there is "absolutely no correlation between the ability of a drug to bind to histamine receptors and its antipsychotic activity." [Tr. 1387-1388 (Roth)] An antipsychotic drug's activity at histamine receptors therefore would be considered "off-target actions that are completely unrelated to their antipsychotic activity." [Tr. 1389 (Roth)]

Defendants introduced no evidence that a person of ordinary skill in the art in 1988 would have selected an antihistamine as a lead compound in the search for a potential antipsychotic. Dr. Press admitted that his own research never sought to develop a compound that would be both an antihistamine and an antipsychotic. [Tr. 242 (Press)] He was unaware of any drug that has ever been approved for use both as an antihistamine and an antipsychotic. [Tr. 242 (Press)] None of Defendants' experts disputed Dr. Roth's testimony that anti-histaminic activity would be considered "off-target" activity in the search for a potential antipsychotic.

The designated portions of a deposition of Dr. Nicholas Bodor taken on September 12, 1984, in connection with a Patent Office interference proceeding involving the '416 patent do not support Defendants' arguments with respect to the unsubstituted butoxy compound. Moreover, Dr. Bodor's deposition testimony is inadmissible hearsay and Defendants have not shown that his testimony falls into any of the exceptions to the hearsay rule. Dr. Bodor testified that antihistamines have central nervous system effects because they generally are sedating. [Tr. 1237 (Roth)] Sedation is not the

same as antipsychotic activity. Thus, Dr. Bodor's testimony does not change the fact that the unsubstituted butoxy compound is described as an antihistamine, not an antipsychotic, in the '416 patent. [Tr. 1237 (Roth)]

In view of the foregoing facts, which are essentially undisputed, the Court concludes that the '416 patent describes the unsubstituted butoxy compound as an antihistamine not an antipsychotic, and thus strongly teaches away from the selection of this compound as a lead compound for antipsychotic drug discovery.

2. The Nakagawa Declaration Teaches Away from Selection of the Unsubstituted Butoxy Compound as a Lead Compound

Recognizing that the '416 patent teaches away from the unsubstituted butoxy compound, Defendants simply disregard the unhelpful teachings of the '416 patent. Instead, they rely solely on a declaration of Dr. Kazuyuki Nakagawa ("the Nakagawa declaration") filed by Otsuka during prosecution of the '416 patent as allegedly suggesting the selection of the unsubstituted butoxy compound as a lead compound. The Nakagawa declaration, however, is not prior art to the '528 patent and therefore is irrelevant to alleged obviousness. [See Section VI.A.3.a. below] Moreover, even if it were prior art, the Nakagawa declaration actually teaches away from the unsubstituted butoxy compound.

a. The Declaration Was Not Intended to Identify Lead Compounds

The Nakagawa declaration described three pharmacologic tests: (1) a guinea pig ileum test for antihistamine activity; (2) a halothane anesthesia increasing activity test; and (3) a test for activity in inhibiting the jumping behavior in mice induced by methamphetamine and L-DOPA ("the mouse jumping test"). [Tr. 1242 (Roth); DTX 214]

The Nakagawa declaration was submitted to the Patent Office to show that the compounds of the invention of the '416 patent were patentable over the prior art. [Tr. 1243 (Roth); Tr. 1638-1639 (Nichols); Tr. 255-256 (Press); DTX 214] The mouse jumping test results were specifically presented to compare the compounds of the invention to prior art compounds D and E. The results showed that, as a group, the compounds of the invention were "substantially more potent in inhibiting mouse jumping than compounds D and E." [Tr. 1243 (Roth); Tr. 1638-1639 (Nichols); Tr. 255-256 (Press); DTX 214] The declaration was not intended to identify potential lead compounds for an antipsychotic research program, and a person of ordinary skill in the art never would have used it for that purpose. Dr. Press, for example, was asked on cross-examination: "Does the declaration attempt to draw any conclusions about which compound of the application, if any, would be the most suitable lead compound in an antipsychotic drug discovery program?" [Tr. 257 (Press)] He responded: "No. That was not the intent of the declaration." [Tr. 257 (Press)]

Defendants' expert Dr. Marshall testified at his deposition that, in his opinion, one of ordinary skill in the art would not choose a lead compound for a drug discovery program based on the limited test data presented in the Nakagawa declaration. [Tr. 688-89 (Marshall)]

There also is no evidence that a person of ordinary skill would have located and relied on a declaration filed with the Patent Office. Dr. Press has never relied on a declaration from a patent prosecution history to select a lead compound for a drug discovery program, and he could identify no scientist who has done so. [Tr. 249 (Press)] Dr. Castagnoli has never personally located a patent prosecution history or cited to a declaration from a prosecution history in any scientific publication. [Tr. 848-49 (Castagnoli)] Defendants' experts did not even personally locate the Nakagawa declaration when forming their opinions. The declaration was provided to them by counsel. [Tr. 248-

249 (Press); Tr. 846 (Castagnoli)] Thus, Defendants failed to prove that a person of ordinary skill in the art would have located and relied upon the Nakagawa declaration to select a lead compound.

b. Mouse Jumping Results Would Have Been Given Little Consideration

Defendants allege that the mouse jumping test in the Nakagawa declaration was used to predict antipsychotic activity. The mouse jumping test, however, has not been widely used as an indicator of potential antipsychotic activity. [Tr. 1243-1244 (Roth)] For example, before they became involved in this case, Dr. Roth and Dr. Nichols had never heard of the mouse jumping test. [Tr. 1243-1244 (Roth); Tr. 1641 (Nichols)] Dr. Roth performed a literature review and found that the test has not been used routinely to test for potential antipsychotic activity. [Tr. 1243-1244 (Roth)] Defendants introduced no evidence to the contrary.

The Nakagawa declaration itself does not describe what activity the mouse jumping test is used to predict. The declaration does not refer to antipsychotic activity or even mention the word "schizophrenia." [Tr. 252-253 (Press)] The declaration refers to a paper by Lal et al. in describing the test procedure for the mouse jumping test. [DTX 214 at 12] Although Defendants' expert Dr. Castagnoli testified that one would want to know the content of that reference to understand the purpose of the mouse jumping test in the Nakagawa declaration [Tr. 850-51 (Castagnoli)], Defendants introduced no evidence at trial concerning this paper. They did not even seek to admit this paper into evidence.

There is no evidence that the mouse jumping test has ever been successfully used to discover any new antipsychotic drug. [Tr. 1244 (Roth); Tr. 253 (Press); Tr. 851-852 (Castagnoli)] Dr. Press could not identify any company presently using the mouse jumping test to screen for potential

antipsychotics. [Tr. 251 (Press)] Dr. Castagnoli could not identify any approved antipsychotic drug that was discovered using the mouse jumping test. [Tr. 851-852 (Castagnoli)] Nor could he identify any approved antipsychotic drugs in which the mouse jumping test was used as the first screening test performed on that compound. [Tr. 852 (Castagnoli)]

The mouse jumping test is not the same as the inhibition of apomorphine-induced stereotypy test. [Tr. 1244 (Roth)] In the mouse jumping test, methamphetamine potentiates the release of dopamine, which increases the synaptic availability of dopamine. [Tr. 1244 (Roth)] In addition, the amount of dopamine that can be released is increased. [Tr. 1244 (Roth)] A compound can have activity in inhibiting mouse jumping through a number of mechanisms. [Tr. 1244-1245 (Roth)] It could inhibit the presynaptic release of dopamine as an autoreceptor agonist or it could interfere in some unknown way with dopaminergic neurotransmission postsynaptically. [Tr. 1244-1245 (Roth)] Thus, contrary to Dr. Castagnoli's incorrect testimony, the mouse jumping test is not a specific test for blockade of postsynaptic D_2 dopamine receptors. [Tr. 1246-1247 (Roth); Tr. 751 (Castagnoli)]

The stereotypy test, on the other hand, is a relatively specific test for compounds that block or attenuate D_2 dopamine receptor signaling postsynaptically. [Tr. 1245 (Roth)] These differences in how the mouse jumping and stereotypy tests work affect the types of compounds they identify. [Tr. 1245 (Roth)] The mouse jumping test may identify autoreceptor agonists or presynaptic agonists whereas the stereotypy test identifies postsynaptic D_2 receptor antagonists. [Tr. 1245 (Roth)] Consequently, the stereotypy test "has been enormously successful" in identifying new antipsychotic compounds whereas the mouse jumping test "has been unsuccessful." [Tr. 1251 (Roth)]

There is no known way to correlate results in the mouse jumping test to results in the stereotypy test. [Tr. 1247 (Roth)] Thus, a person of ordinary skill in the art in October 1988 would

have been unable to correlate results in the mouse jumping test to results in the stereotypy test. [Tr. 1247-1248, 1250-1251 (Roth)] Dr. Marshall speculated that such a correlation could be made, but he subsequently admitted on cross-examination that he never attempted to make such a correlation in this case. [Tr. 2203 (Marshall)] His testimony is therefore unpersuasive.

c. A Person of Ordinary Skill Would Have Selected the Most Potent Compound

Even assuming that a person of ordinary skill in the art wanted to select a lead compound using the mouse jumping results of the Nakagawa declaration, he or she would have selected the most potent compound, which was compound 44. [Tr. 1639-40 (Nichols); Tr. 1252 (Roth)] The most potent compound would have been selected to reduce the chance of activating off-target receptors or producing toxicity. [Tr. 1639-40 (Nichols); Tr. 1252 (Roth); Tr. 263 (Press)] In addition, from an economic perspective, highly potent drugs are less expensive to manufacture and dispense as medications. [Tr. 1640 (Nichols)]

Dr. Roth and Dr. Nichols both testified that compound 44 would have been selected as the lead compound, assuming one wanted to rely on the declaration to choose a lead compound. Dr. Roth explained that compound 44 was "by far and away the most potent compound" evaluated in the mouse jumping test and was "the only compound that [was] sub-milligram per kilogram in potency." [Tr. 1253 (Roth)] Dr. Nichols similarly testified that compound 44 was "by far the most potent compound in that series of compounds" evaluated in the mouse jumping test. [Tr. 1640 (Nichols)] Defendants failed to rebut this testimony.

The unsubstituted butoxy compound was compound 41 in the Nakagawa declaration. [Tr. 1642 (Nichols)] The reported ED_{50} value for the unsubstituted butoxy compound in the mouse

jumping test was 5.5 milligrams per kilogram. [Tr. 1643 (Nichols)] By contrast, the reported ED_{50} value for compound 44 in the mouse jumping test was 0.53 milligrams per kilogram. [Tr. 1643 (Nichols)] Compound 44 was therefore approximately ten times more potent in the mouse jumping test than the unsubstituted butoxy compound. [Tr. 1643-44 (Nichols); Tr. 262 (Press)] Dr. Press conceded that this difference in potency was "certainly worthy of note." [Tr. 262 (Press)] Dr. Marshall similarly testified during his deposition that "[t]he results that are presented in Table 8 suggest that the most potent of these compounds is test compound 44." [Tr. 692 (Marshall)] Dr. Castagnoli stated that a person of ordinary skill "would have been very excited about the result reported [for compound 44] in the Nakagawa declaration." [Tr. 857 (Castagnoli)] Defendants introduced no evidence that a person of ordinary skill in the art would have disregarded this ten-fold difference in potency.

Compound 44 was a 5-position isomer with a propoxy linker and 2-ethoxy substituted phenyl ring. [Tr. 1642-1643 (Nichols); Tr. 261-262 (Press)] It therefore differed structurally from the unsubstituted butoxy compound, which was a 7-position isomer with a butoxy linker and no substitution on the phenyl ring. [Tr. 1643 (Nichols)] In view of the differences in structure and potency between these compounds, the Nakagawa declaration teaches away from the unsubstituted butoxy compound. [Tr. 1644 (Nichols)]

There is no reason that one of ordinary skill in the art would have disregarded the most potent compound in the Nakagawa declaration, compound 44. [Tr. 1254 (Roth)] Defendants' expert Dr. Press asserted during discovery that compound 44 would have been disregarded because it had beta-adrenergic activity that would cause the unwanted side effect of orthostatic hypotension. [Tr. 266 (Press)] He subsequently admitted, however, that his opinion was incorrect:

Q. Does beta-adrenergic activity cause orthostatic hypotension?

A. No, it does not.

Q. So your report was incorrect on that point?

A. Clearly, that was mistakenly written.

[Tr. 265-267 (Press)] Dr. Press also admitted that the compounds of the Nakagawa declaration lacked a 2-hydroxy substituent, a common feature of beta-blockers. [Tr. 267-268 (Press)] Defendants have now withdrawn any reliance on Dr. Press's erroneous arguments for disregarding compound 44.

Unable to rely on Dr. Press's flawed "beta-blocker" theory, Defendants now raise a new argument for disregarding compound 44. They allege that one of ordinary skill would have avoided compound 44 because it contained an ethoxy substituent. Defendants base this assertion on the anti-epinephrine lethality data for compound 12 at column 44 of U.S. Patent No. 4,619,932 ("the '932 patent"). The Court disagrees that the '932 patent would have led one of ordinary skill to avoid all ethoxy-substituted compounds. The '932 patent did not disclose compound 44 or any testing on compound 44. [DTX 20] Compound 12 of the '932 patent differed significantly in structure from compound 44 of the Nakagawa declaration. Compound 12 was a 6-position isomer with an all-carbon linker whereas compound 44 was a 5-position isomer with a propoxy linker. [Tr. 1643, 1646-1648 (Nichols)] Otsuka established at trial that even "a minor structural difference can make a huge difference in the pharmacology" of a compound. [Tr. 1650-51 (Nichols)] A person of ordinary skill therefore would have looked at the entire structure of compound 12 and would not have assumed that its anti-epinephrine activity was due to the 2-ethoxy substituent. [Tr. 1285-1292 (Roth); DTX 20] Defendants' assertion to the contrary is based on speculation.

Further, Dr. Nichols confirmed, without dispute by Defendants, that there was no published information available before October 31, 1988, suggesting that compound 44 would have cardiovascular side effects. [Tr. 1644 (Nichols)] The Court therefore concludes that a person of ordinary skill in the art would have selected compound 44 over the much less potent unsubstituted butoxy compound as a lead compound for antipsychotic drug discovery.

3. A Person of Ordinary Skill Would Have Chosen More Potent Compounds of the '932 Patent Over the Unsubstituted Butoxy Compound

Otsuka's '932 patent, which issued on October 28, 1986, discloses carbostyril derivatives that are 6-position isomers having alkyl (all-carbon) linkers. [Tr. 1646-47; 1667-68 (Nichols); DTX 20] The '932 patent provides mouse jumping data for a number of these compounds at column 43. [Tr. 1646-48 (Nichols); DTX 20] Defendants do not dispute that the protocol for the mouse jumping test in the '932 patent is identical to the protocol for the same mouse jumping test described in the Nakagawa declaration. [Tr. 1669 (Nichols)]

There is no reason that a person of ordinary skill in the art in October 1988 would have selected the unsubstituted butoxy compound of the Nakagawa declaration over the compounds of the '932 patent as a lead compound in an antipsychotic drug discovery program. [Tr. 1669 (Nichols)]

In Table 2 at column 43 of the '932 patent, most of the compounds of the '932 patent evaluated in the mouse jumping test had an ED_{50} value that was significantly lower (more potent) than the 5.5 mg/kg ED_{50} value of the unsubstituted butoxy compound in the Nakagawa declaration. [Tr. 1669 (Nichols); DTX 214; DTX 20] Compound No. 3 in the '932 patent, for example, had an ED_{50} value in the mouse jumping test of 1.05 mg/kg, which was five times more potent than the unsubstituted butoxy compound. [DTX 20 at col. 43] Defendants provided no reason why one of

ordinary skill would have disregarded Compound No. 3 as a potential lead compound. Defendants' "avoid ethoxy substituents" argument cannot apply because Compound No. 3 and many other compounds in the '932 patent have no ethoxy substituent. [DTX 20 (cols. 41-42)]

Because many of the '932 patent compounds were significantly more potent than the unsubstituted butoxy compound in the mouse jumping test, a person of ordinary skill in the art in October 1988 relying on mouse jumping data would have chosen one of the more potent compounds of the '932 patent over the less potent unsubstituted butoxy compound. [Tr. 1646, 1668-70 (Nichols)] It would have been illogical for such person to engage in speculative research to attempt to increase the potency of the unsubstituted butoxy compound when significantly more potent compounds were already disclosed in the '932 patent. Accordingly, the '932 patent would have led one of ordinary skill away from the unsubstituted butoxy compound.

For all these reasons, the Court finds that Defendants have failed to prove that a person of ordinary skill in the art in October 1988 would have selected the unsubstituted butoxy compound as a lead compound for an antipsychotic drug discovery program over other compounds in the prior art, including clozapine-like compounds, risperidone-like compounds, compound 44 of the Nakagawa declaration, and the compounds of the '932 patent. Defendants' obviousness and obviousness-type double patenting defenses based on the unsubstituted butoxy compound therefore cannot succeed.

F. The Prior Art Fails to Suggest Modifying the Unsubstituted Butoxy Compound to Obtain Aripiprazole

Even assuming incorrectly that a person of ordinary skill in 1988 would have been interested in carbostyril derivatives as potential antipsychotics, and also assuming incorrectly that such a person somehow would have selected the unsubstituted butoxy compound as a lead compound rather than

one of the hundreds of other specifically identified carbostyril derivatives in the prior art, there still is no prior art teaching that would have led such a person to modify the structure of the unsubstituted butoxy compound to obtain aripiprazole.

There are thousands, if not millions, of ways that the unsubstituted butoxy compound could have been modified. [Tr. 1617-24 (Nichols)] Only one particular combination of structural modifications (substituting chlorine substituents at both the 2 and 3 positions of the phenyl group) would have led to aripiprazole. No prior art, however, suggested making those or any other modifications to the unsubstituted butoxy compound. Given the high level of unpredictability of antipsychotic drug research, there would have been no reasonable expectation of success with respect to any potential modification of this compound.

1. The '416 Patent Does Not Suggest Modifying the Unsubstituted Butoxy Compound

Defendants do not address or even cite the '416 patent in the portion of their proposed findings concerning modification of the unsubstituted butoxy compound. The '416 patent would not have led a person of ordinary skill in the art in October 1988 to aripiprazole. [Tr. 1617-1637 (Nichols); Tr. 1207-1225 (Roth); DTX 6] To the contrary, the '416 patent specifically identifies the unsubstituted butoxy compound as an antihistamine, not an antipsychotic, and excludes it from claims directed to central nervous system controlling agents. [Tr. 1630-1636 (Nichols); Tr. 1225 (Roth)] Because the '416 patent describes the unsubstituted butoxy compound as an antihistamine, there would have been no reason to move it forward as an antipsychotic drug. [Tr. 1225 (Roth); Tr. 1635-1637 (Nichols)]

The '416 patent is devoid of any suggestion to add chlorine atoms at the 2 and 3 positions of the phenyl ring of the unsubstituted butoxy compound to convert it from an antihistamine to an antipsychotic. [DTX 6] The first paragraph of column 4 of the '416 patent describes numerous specific examples of phenyl rings for the carbostyril derivatives, including an unsubstituted phenyl ring and many different substituted phenyl rings. [Tr. 1624 (Nichols); DTX 6] None of those exemplified phenyl rings, however, is a 2,3-dichloro substituted phenyl ring as present in aripiprazole. [Tr. 1624-25 (Nichols); Tr. 231 (Press)] If a person of ordinary skill in the art in October 1988 were relying on the '416 patent to design an antipsychotic compound, there is no reason that person would have excluded the numerous exemplified substituted phenyl rings described at column 4 of the patent. [Tr. 1625 (Nichols)] In fact, *none* of the 500 specific exemplary carbostyril compounds disclosed in the '416 patent has a 2,3-dichloro substituted phenyl ring. [DTX 6; Tr. 233 (Press)] Defendants offered no evidence to the contrary. The absence of any teaching of a 2,3-dichloro substituted phenyl ring in the '416 patent refutes Defendants' argument that it would have been obvious to convert the unsubstituted butoxy compound to aripiprazole. Rather, the lack of any such disclosure strongly teaches away from aripiprazole.

2. Chlorination Is Not Required for Antipsychotic Activity

A person of ordinary skill in the art in October 1988 would have understood that chlorine substitution is not required for antipsychotic activity. [Tr. 1656, 1662 (Nichols)] Many antipsychotics lacking any chlorine substituent were known before October 1988. Examples of antipsychotics known before October 1988 that had no chlorine substituent include fluphenazine, trifluoperazine, thiothixene, thioridazine, risperidone, flupentixol, pimozide, mesoridazine, sulforidazine, fluspirilene, benperidol, pipamperone, droperidol, bromperidol, trifluperidol, spiperone,

acetophenazine, sulpiride, pericyazine, melperone, and amisulpride. [Tr. 1658-59 (Nichols); PTX 305; PTX 306; PTX 436; PTX 453; PTX 786; PTX 784; DTX 990; DTX 409; PTX 469] Because many clinically effective antipsychotics lack any chlorine substituent, a person of ordinary skill in October 1988 would not have believed that chlorine substitution was necessary for antipsychotic activity. [Tr. 1662 (Nichols)] Defendants introduced no evidence to the contrary.

Chlorine is an electronegative atom. [Tr. 1656 (Nichols)] Many antipsychotics have electronegative groups that are not chlorine or have no chlorine or other electronegative group at all. [Tr. 1656 (Nichols)] Examples of non-chlorine electron-withdrawing substituents include fluorine, trifluoromethyl, sulfonamide, and sulfoxide. [Tr. 1662 (Nichols)]

The prior art fails to suggest any expected improvement in properties from chlorination. Dr. Press, for example, has authored prior art papers in which chlorination reduced or completely eliminated a compound's potential antipsychotic activity. [Tr. 297-300, 302-304 (Press); PTX 114, PTX 296] In the Defendants' contested facts section of the parties' Pretrial Order, Defendants argued that one of ordinary skill would have chlorinated the unsubstituted butoxy compound to increase its penetration through the blood-brain barrier. [Pretrial Order, D.I. 362, pages 88-89, ¶¶ 85-86] At trial, however, Dr. Press admitted that he was unaware of any evidence that the unsubstituted butoxy compound had any difficulty penetrating the blood brain barrier. [Tr. 286 (Press)] Defendants have now dropped this argument.

There was no known antipsychotic drug in 1988 that had chlorine atoms substituted at both the 2 and 3 positions of a phenyl ring. [Tr. 1663-65 (Nichols)] No known antipsychotic drug even had two adjacent chlorine atoms substituted anywhere on a phenyl ring. [Tr. 1663-65 (Nichols)] As Dr. Nichols explained: "There was no known antipsychotic drug, successful or otherwise, that had

those two particular substituents arranged in a 2,3 or, indeed, in an adjacent orientation." [Tr. 1665 (Nichols)] Defendants introduced no evidence to the contrary. Aripiprazole appears to be the only antipsychotic drug with a 2,3-dichloro substituted phenyl ring that has ever been approved by the FDA. [Tr. 1527 (Nichols); Tr. 192 (Press); Tr. 820 (Castagnoli)] Because antipsychotics with a 2,3-dichloro substituted phenyl ring were unknown in 1988, it would not have been obvious to make an antipsychotic with a 2,3-dichloro substituted phenyl ring. [Tr. 1664-1665 (Nichols)]

There was no scientific basis for a person of ordinary skill in the art in October 1988 to have reasonably expected that chlorinating the unsubstituted butoxy compound at the 2 and 3 positions of the phenyl ring would yield a clinically effective, safe atypical antipsychotic. [Tr. 1665-66 (Nichols)] It therefore would not have been obvious in October 1988 for a person of ordinary skill to make an antipsychotic with a 2,3-dichloro substituted phenyl ring. [Tr. 1664-65 (Nichols)]

3. The Nakagawa Declaration Does Not Suggest Modifying the Unsubstituted Butoxy Compound

Defendants argue that one of ordinary skill in the art would have modified the unsubstituted butoxy compound based on "structure-activity relationship" (SAR) information allegedly provided by the mouse jumping results in the Nakagawa declaration. Even though no 2,3-dichloro substituted antipsychotic is disclosed in the declaration [Tr. 259 (Press)], they attempt to extract a teaching toward a 2,3-dichloro from the data. As explained above, however, the purpose of the Nakagawa declaration was to show that the compounds of the '416 patent were superior to prior art compounds in the mouse jumping test. [Tr. 1638-39 (Nichols); Tr. 255-57 (Press)] It was not intended as a comparison of the compounds of the '416 patent against each other as Defendants' SAR analysis proposes. Dr. Press acknowledged on cross-examination that none of the SAR conclusions he drew

from the Nakagawa declaration were stated anywhere in the declaration. [Tr. 256-57 (Press); DTX 214] Defendants never explained how their SAR arguments make any sense in the context of the prosecution history of the '416 patent. The Court concludes that Defendants' SAR arguments take the declaration entirely out of context.

The Nakagawa declaration would not have led a person of ordinary skill in the art in October 1988 to select and then modify the unsubstituted butoxy compound to arrive at aripiprazole. [Tr. 1666 (Nichols)] The unsubstituted butoxy compound was not the most potent compound in the declaration, and the '416 patent described it as an antihistamine. [Tr. 1666-67 (Nichols)] The most potent compound reported in the Nakagawa declaration, compound 44, does not contain any chlorines. [Tr. 1640, 1642 (Nichols)] Further, there was "no teaching in the Nakagawa declaration that would point you to a 2,3-dichloro as somehow producing antipsychotic activity in that molecule." [Tr. 1667 (Nichols)]

A person of ordinary skill in the art who was interested in relying on the mouse jumping data of the Nakagawa declaration would have selected compound 44 as a lead compound over the unsubstituted butoxy compound. [Tr. 1639-40 (Nichols); Tr. 1252 (Roth)] Compound 44 was about ten times more potent than the unsubstituted butoxy compound (compound 41). [Tr. 1643-44 (Nichols); Tr. 262 (Press)] It would have been illogical for a person of ordinary skill to engage in a speculative research program aimed at trying to increase the potency of the unsubstituted butoxy compound when they already had a compound, compound 44, that was ten times more potent than the unsubstituted butoxy compound.

The Nakagawa declaration only evaluated compounds having an unsubstituted or monosubstituted phenyl ring in the mouse jumping test. [Tr. 1653 (Nichols); Tr. 259 (Press)] Thus,

if a person of ordinary skill in the art in October 1988 were relying on the Nakagawa declaration to design an antipsychotic, there is no reason that person would have excluded unsubstituted and monosubstituted compounds. [Tr. 1653-54 (Nichols)] No carbostyril derivatives having two or three substituents on the phenyl ring were evaluated in the mouse jumping test even though the application leading to the '416 patent specifically disclosed such compounds. [Tr. 259- 261 (Press); DTX 6] The Nakagawa declaration therefore taught toward unsubstituted or monosubstituted compounds and away from disubstituted compounds such as aripiprazole with its unique 2,3-dichloro substituted phenyl ring.

Eight of the nine compounds evaluated in the mouse jumping test in the Nakagawa declaration had a propoxy linker. [Tr. 1653 (Nichols); Tr. 258 (Press)] If a person of ordinary skill in the art in October 1988 were relying on the Nakagawa declaration to design a potential antipsychotic, there is no reason that person would have excluded propoxy-linked compounds. [Tr. 1653 (Nichols)] Thus, the declaration teaches toward propoxy-linked compounds and away from any modification of the unsubstituted butoxy compound.

The mouse jumping data presented in the Nakagawa declaration do not support Defendants' SAR arguments. Defendants argue that a propoxy-linked compound having a 2-chloro substituent (compound 43), and another propoxy-linked compound having a 3-chloro substituent (compound 39), were more potent in the mouse jumping test than an unsubstituted propoxy-linked compound (compound 6). They then ask the Court to assume, with no supporting data, that (1) a hypothetical propoxy-linked compound combining both the 2-chloro and 3-chloro substituents would have even greater potency than compounds 43 and 39; and (2) a person of ordinary skill would then apply that alleged teaching of a 2,3-dichloro substitution pattern in a hypothetical propoxy-linked compound to

the unsubstituted butoxy compound. There is no support for this argument. Otsuka established that even small molecular changes can have a major effect on pharmacology. [*See, e.g.*, Tr. 1173 (Roth); Tr. 1554-56 (Nichols)] Defendants introduced no test data, scientific publications, or other evidence to prove that one of ordinary skill in the art would have reasonably expected the effects of adding chlorine substituents to be additive. Nor did Defendants prove that it would have been reasonable to simply assume that any SAR information from the propoxy-linked series of compounds in the Nakagawa declaration likely would translate to the unsubstituted butoxy compound.

Dr. Press did not run any tests of his own on the compounds of the Nakagawa declaration. [Tr. 269 (Press)] Nor did he ask Defendants' experts Dr. Beninger or Dr. Marshall to run any tests. [Tr. 269 (Press)] Defendants have no evidence whatsoever of how potent aripiprazole would be in the mouse jumping test. [Tr. 269 (Press)] For all Defendants established, aripiprazole could be completely inactive in the mouse jumping test, in which case a person of ordinary skill presumably would have discarded it even if they had made and tested it in the mouse jumping test as Defendants propose.

Similarly, Defendants failed to cite any test data or scientific publication to support Dr. Press's speculation that a 2,3-dichloro di-substituted carbostyril derivative would be expected to be more potent than the 2-chloro or 3-chloro mono-substituted compounds evaluated in the mouse jumping test in the Nakagawa declaration. [Tr. 167-168 (Press)] No evidence supports such a conclusion. The Banno article, for example, specifically concluded that "the introduction of dichloro substitution at the 2 and 3 positions on the phenyl ring in the phenylpiperazinyl moiety significantly reduced the activity" in the mouse jumping test of compound Vc-17, which was the 2,3-dichloro propoxy-linked compound. [DTX 84 at 4385] This 2,3-dichloro substituted compound had an ED_{50} value in the

mouse jumping test of 37.4 mg/kg, far less potent than the other compounds tested. [DTX 84 at 4384 (Table III)] If Dr. Press's "additive effect" idea were correct, this compound should have been highly potent in the mouse jumping test, but it was not. Although the Banno article was published in November 1988 and thus is not prior art, it shows that Dr. Press's "additive effect" assertion is scientifically untenable and confirms Otsuka's undisputed evidence that small molecular changes can cause unpredictable changes in biological activity, particularly with respect to potential antipsychotic drugs. The Court therefore declines to accept Dr. Press's unsupported testimony concerning an alleged "additive effect" for chlorine atoms.

Despite having a clear-and-convincing evidence burden of proof, Defendants elected to perform no testing and have no scientific evidence to support their obviousness arguments. As such, Defendants' assertion that it would have been obvious to use the mouse jumping test to discover aripiprazole—when that test has never been used to discover any antipsychotic—is based on pure speculation.

The Court concludes that it would not have been possible for a person of ordinary skill in the art in October 1988 to identify aripiprazole as a potential antipsychotic based on the information in the Nakagawa declaration. [Tr. 1651-1652 (Nichols)] Nothing in the declaration would have led a person of ordinary skill in the art to modify the structure of the unsubstituted butoxy compound to arrive at aripiprazole with a reasonable expectation that it would be a clinically effective antipsychotic drug. [Tr. 1651-1652 (Nichols)]

4. The SE '945 Application Does Not Suggest Modifying the Unsubstituted Butoxy Compound

Defendants argue that a Swedish patent application ("the SE '945 application") related to the '416 patent supports their arguments for modification of the unsubstituted butoxy compound. [DTX 1159T] The SE '945 application, however, like the '416 patent, fails to describe the unsubstituted butoxy compound as an antipsychotic or suggest that it would be a suitable lead compound for antipsychotic drug discovery. There is no disclosure in the SE '945 application that would have led a person of ordinary skill in the art in October 1988 to select and then modify the unsubstituted butoxy compound to arrive at aripiprazole. [Tr. 1692 (Nichols)] Not one word in the SE '945 application suggests modifying the unsubstituted butoxy compound in any way. [DTX 1159T]

Defendants argue that the SE '945 application "reports that a 2,3-dichloro substitution on the phenyl ring of an unsubstituted propoxy compound led to a compound reported to have antischizophrenic activity." [Def. FOFCOL, page 45] Contrary to Defendants' misleading assertion, there is no suggestion in the SE '945 application that any "unsubstituted propoxy compound" was modified to include a 2,3-dichloro substituted phenyl ring. The 2,3-dichloro propoxy compound is simply listed in the SE '945 application among dozens of other carbostyril derivatives. [Tr. 1690 (Nichols)] There are no pharmacological data or other information in the SE '945 application that would have led a person of ordinary skill in the art to conclude that the 2,3-dichloro propoxy compound is an antipsychotic. [Tr. 1688-1690 (Nichols)] The SE '945 application provides no experimental data at all relating to potential antipsychotic activity. [Tr. 1689 (Nichols); Tr. 217-218 (Press)] There is no information of any kind in the SE '945 application that would have informed a

person of ordinary skill in the art in October 1988 as to which of the specifically identified compounds, if any, would have antipsychotic activity. [Tr. 1689-90 (Nichols); Tr. 218-219 (Press)]

Additional proposed findings with respect to the SE '945 application are set forth in section IV.I below.

5. The Hiyama Abstract Does Not Suggest Modifying the Unsubstituted Butoxy Compound

Defendants further argue that a 1981 publication ("the Hiyama abstract") disclosing another Otsuka carbostyril derivative, OPC-4139, supports their arguments for modification of the unsubstituted butoxy compound. There is no basis for this assertion.

OPC-4139 had a propoxy linker, not a butoxy linker like aripiprazole. [Tr. 1683 (Nichols); Tr. 305 (Press)] If a person of ordinary skill in the art in October 1988 were relying on the Hiyama abstract to design a potential antipsychotic, there is no reason that person would have excluded propoxy-linked compounds because OPC-4139 was a propoxy-linked compound. [Tr. 1686 (Nichols)] The abstract teaches toward a propoxy-linked compound. [Tr. 1686 (Nichols); DTX 514]

In addition, OPC-4139 was monosubstituted; it had a single chlorine atom at the 3 position of the phenyl ring. [Tr. 1683 (Nichols)] OPC-4139 did not have a 2,3-dichloro substituted phenyl ring like aripiprazole. [Tr. 305 (Press)] If a person of ordinary skill in the art in October 1988 were relying on the Hiyama abstract to design a potential antipsychotic, there is no reason that person would have excluded monosubstituted compounds. [Tr. 1684 (Nichols)]

The Hiyama abstract does not disclose aripiprazole. [Tr. 305 (Press)] It would not have been possible for a person of ordinary skill in the art in October 1988 to identify aripiprazole as a potential antipsychotic based on the Hiyama abstract. As Dr. Nichols explained: "The Hiyama abstract, first

of all, talks about propoxy linked compounds, and it indicates a monosubstituted 3-chloro phenyl ring. And there's no indication that you should do anything to change this to move it toward aripiprazole." [Tr. 1683-84 (Nichols)]

There is no disclosure in the Hiyama abstract that would have led a person of ordinary skill in October 1988 to select and then modify the unsubstituted butoxy compound to arrive at aripiprazole. The abstract does not even mention the unsubstituted butoxy compound. [Tr. 1686-1687 (Nichols)]

The Hiyama abstract describes results of OPC-4139 in several animal studies. OPC-4139 inhibited the jumping behavior of mice induced by L-DOPA and methamphetamine, blocked the lethal effective methamphetamine in grouped mice, and inhibited fighting behavior in isolated mice. [DTX 514] OPC-4139 also inhibited methamphetamine-induced rotational behavior of rats, avoidance behavior in rats, and apomorphine-induced climbing behavior of mice. [DTX 514] OPC-4139 did not antagonize apomorphine-induced stereotypy and exhibited no cataleptogenic activity in rats. [DTX 514; Tr. 306 (Press)] Certain biochemical changes were also measured. [Tr. 1280-1281 (Roth); DTX 514] Because inhibition of apomorphine-induced stereotypy is highly correlated with antipsychotic activity, and OPC-4139 did not inhibit apomorphine-induced stereotypy, the Hiyama abstract did not indicate that the compound had antipsychotic activity. [Tr. 1281 (Roth)]

The fact that OPC-4139 was inactive in inhibiting apomorphine-induced stereotypy would indicate that it was inactive at postsynaptic D_2 dopamine receptors. [Tr. 1282 (Roth); DTX 514] A compound that is inactive at postsynaptic D_2 dopamine receptors will not have antipsychotic effect. [Tr. 1282 (Roth)]

Aripiprazole and OPC-4139 do not share similar pharmacologic properties. As Dr. Roth explained, the compounds are "quite distinct." [Tr. 1284-1285 (Roth)] OPC-4139, unlike aripiprazole, appears to be a presynaptic agonist or autoreceptor agonist that is essentially devoid of postsynaptic D_2 antagonist activity. [Tr. 1284-1285 (Roth)] On rebuttal, Dr. Marshall testified that a worker of ordinary skill in the art, looking at the data in the Hiyama abstract would have considered OPC-4139 ("this drug") to have D2 antagonist action. [Tr. 2188 (Marshall)] However, as admitted by Dr. Marshall, there are no publications expressing such a view. [2203-2204 Marshall]

The Hiyama abstract on OPC-4139 would not have led a person of ordinary skill in the art in October 1988 toward aripiprazole. [Tr. 1285 (Roth); DTX 514] If anything, the abstract suggests making other compounds that are presynaptic autoreceptor agonists. [Tr. 1285 (Roth); DTX 514] That approach would not have led to aripiprazole. [Tr. 1285 (Roth); DTX 514]

OPC-4139 never became an approved antipsychotic drug. [Tr. 1282 (Roth); Tr. 307 (Press)]

G. A Person of Ordinary Skill Would Not Have Selected OPC-4392 as a Lead Compound

Unlike Teva/Barr's experts, Defendant Apotex's expert Dr. Castagnoli chose OPC-4392 as the lead compound, not the unsubstituted butoxy compound. For all the reasons set forth in Section IV.D.1 above, however, the prior art reported OPC-4392's failure in clinical trials before October 1988. OPC-4392 lacked efficacy against positive symptoms, activated schizophrenia patients in a potentially dangerous manner, and caused "mental anguish" and other potentially serious neuropsychiatric side effects even at low doses. [Tr. 1190-1191 (Roth); PTX 545] One of ordinary skill in the art in October 1988 therefore would have avoided OPC-4392 as a potential lead compound.

Dr. Castagnoli was unqualified to provide any rebuttal testimony to Dr. Roth's testimony concerning the clinical failure of OPC-4392. Dr. Castagnoli is not a psychiatrist or medical doctor of any kind and has no clinical experience in evaluating the efficacy or side effects of antipsychotic medications in humans. [Tr. 829-830 (Castagnoli)] His testimony concerning alleged "attractive properties" of OPC-4392 therefore is entitled to no weight. [*See, e.g.,* Tr. 753 (Castagnoli)] Further, his speculative testimony that OPC-4392 simply needed "to be pumped up in terms of its antipsychotic properties" is unsupported by any scientific evidence that one of ordinary skill in the art would have known how to "pump up" antipsychotic activity. [Tr. 753 (Castagnoli)] Given the unpredictable nature of antipsychotic drug discovery in the 1980s and the high failure rate, researchers clearly did not know how to reliably "pump up" the antipsychotic activity of any compound.

In addition, for the reasons set forth in Sections IV.B and IV.C above, one of ordinary skill in the art in October 1988 would not have selected OPC-4392 as a lead compound over clozapine-like compounds, risperidone-like compounds, compound 44 of the Nakagawa declaration, or the compounds of the '932 patent. Defendants provided no evidence to the contrary. For example, Defendants identified no instance in which any antipsychotic research group ever selected a compound that failed in clinical trials as a lead compound for further investigation. Otsuka itself did not select OPC-4392 as a lead compound for further research after the compound failed. Instead, Dr. Oshiro decided that Otsuka needed to effectively start over by re-screening the 4000 series of compounds to try to identify a compound that, unlike OPC-4392, potently inhibited apomorphine-induced stereotypy in mice. [Tr. 1750-1756 (Oshiro)]

Accordingly, because there would have been no reason for one of ordinary skill in the art in October 1988 to select OPC-4392 as a lead compound for a drug discovery program, Apotex's obviousness arguments based on OPC-4392 cannot succeed.

H. The Prior Art Does Not Suggest Modifying OPC-4392 to Obtain Aripiprazole

OPC-4392 and aripiprazole differ in their chemical structures in several respects. Aripiprazole is a dihydrocarbostyril having a butoxy linker and a 2,3-dichloro substituted phenyl ring. [Tr. 1615 (Nichols)] OPC-4392 is a carbostyril having a propoxy linker and a 2,3-dimethyl substituted phenyl ring. [Tr. 1614-15 (Nichols)]

Thus, to arrive at aripiprazole from OPC-4392, one of ordinary skill in the art would have had to (1) change OPC-4392's carbostyril core to a dihydrocarbostyril; (2) change OPC-4392's propoxy linker to a butoxy linker; (3) change OPC-4392's 2-methyl substituent to a 2-chloro substituent; and (4) change OPC-4392's 3-methyl substituent to a 3-chloro substituent, while concurrently disregarding all the other thousands or millions of other ways that OPC-4392 could have been modified. No prior art, however, suggests modifying OPC-4392 in this manner to arrive at aripiprazole. [Tr. 1616 (Nichols)] The several molecular changes needed to convert OPC-4392 to aripiprazole are simply not described in the prior art. [Tr. 1616 (Nichols)] Dr. Press conceded that he was unaware of any research group that had ever attempted to modify the structure of OPC-4392 to try to convert it to a clinically effective antipsychotic drug. [Tr. 285 (Press)]

In Dr. Castagnoli's opinion, one of ordinary skill in the art seeking to develop a new antipsychotic drug in October 1988 would have chosen OPC-4392 as a lead compound. [Tr. 823 (Castagnoli)] Dr. Castagnoli testified, however, that, in addition to OPC-4392 and the compounds of the Nakagawa declaration, there probably were 100 other starting points that one of skill in the art

in October 1988 could have chosen in seeking to develop a new antipsychotic drug. [Tr. 829 (Castagnoli)] Defendants never established that OPC-4392 would have been selected as a lead compound over those many other potential starting points.

Dr. Castagnoli acknowledged that all of the structural features of OPC-4392 are associated with its clinical profile and side-effect profile and that the prior art did not describe which changes to OPC-4392's structure could be made without negatively impacting its side-effect profile. [Tr. 841 (Castagnoli)]

Dr. Castagnoli offered his opinion during discovery that one of ordinary skill seeking to improve on OPC-4392 in 1988 would have sought to "tune down" its autoreceptor agonist action. He conceded, however, that one of ordinary skill would have had no expectation that any particular structural change would "tune down" OPC-4392's autoreceptor agonist activity. [Tr. 841-44 (Castagnoli)] Defendants never proved that any particular structural change to OPC-4392 would "tune down" its autoreceptor agonist action.

1. The Wise Poster Does Not Suggest Modifying OPC-4392

Defendants rely heavily on the Wise poster as allegedly suggesting structural modifications to OPC-4392 that would have led to aripiprazole. [DTX 398] They failed to prove, however, that the Wise poster is prior art and thus the poster is irrelevant to alleged obviousness. [*See* Section VI.A.3.b below.] Even if the Wise poster were prior art, however, it actually teaches away from aripiprazole.

The Wise poster does not describe aripiprazole or any other carbostyril derivative. [Tr. 1671 (Nichols); Tr. 1259 (Roth); DTX 398] Rather, it describes "coumarins," which are not the same as carbostyril derivatives. [Tr. 1670 (Nichols); Tr. 1259 (Roth); DTX 398] Coumarins have an oxygen atom in place of the nitrogen atom in carbostyrils. [Tr. 1670 (Nichols)] A person of ordinary skill

in the art in October 1988 would not have assumed that the biological properties of coumarins would translate to carbostyril derivatives. [Tr. 1671 (Nichols)] The nitrogen in carbostyrils could donate a hydrogen bond whereas the oxygen in coumarins could accept one. [Tr. 1671 (Nichols)] Those differences in the heterocyclic ring system suggest that the biological properties of coumarins and carbostyril derivatives may not be parallel. [Tr. 1671 (Nichols)] Defendants introduced no evidence to the contrary.

If a person of ordinary skill in the art were relying on the Wise poster in October 1988 to design an antipsychotic, as Defendants contend, there is no reason that person would have excluded coumarins. [Tr. 1677 (Nichols)] Defendants failed to explain why a person of ordinary skill interested in the Wise poster would not have pursued coumarins rather than carbostyril derivatives as potential antipsychotics, particularly when carbostyril derivatives are not even described in the poster.

The Wise poster describes these coumarins as a new class of dopamine autoreceptor agonists. [DTX 398] The autoreceptor agonist hypothesis of atypical antipsychotic drug action was the idea that drugs could selectively target autoreceptors in the brain, and that one could make an autoreceptor agonist that would inhibit the release of dopamine. [Tr. 1259-1260 (Roth)] With less dopamine available to activate dopamine receptors, dopaminergic neurotransmission would be reduced so as to treat schizophrenia. [Tr. 1259-1260 (Roth); Tr. 1672, 1675-1676 (Nichols)] By 1988, however, the autoreceptor agonist hypothesis "had been tested with numerous compounds," including minus PPP, terguride, and low dose apomorphine, "and all of those compounds failed in treating schizophrenia." [Tr. 1283 (Roth)]

Unlike the other hypotheses of atypical antipsychotic drug action, the autoreceptor agonist hypothesis was not based on clozapine's pharmacology. [Tr. 1260-1261 (Roth)] Aripiprazole does not fit within the autoreceptor hypothesis, just as it does not fit within the other hypotheses of atypical antipsychotic drug action. [Tr. 1261 (Roth)] Defendants thus failed to prove that aripiprazole fit within any working hypothesis of atypical antipsychotic drug action that researchers were pursuing in the 1980s.

In his testimony, Dr. Castagnoli attempted to discern teachings in the Wise poster toward D_2 antagonism, which he speculated would allow one to "pump up" the antipsychotic activity of OPC-4392. [Tr. 753-754 (Castagnoli)] There is no suggestion in the Wise poster, however, that Parke-Davis was looking for antagonists at D_2 dopamine receptors. [DTX 398] Consistent with the fact that Parke-Davis was pursuing autoreceptor agonists, not D_2 dopamine receptor antagonists, the Wise poster does not describe any screening of compounds using the inhibition of apomorphine-induced stereotypy test or any other screening test for D_2 antagonism. [Tr. 1261 (Roth)] Parke-Davis nowhere suggests in the poster that any of the tested compounds are D_2 antagonists. [Tr. 1261 (Roth)]

The Wise poster identifies a preferred lead compound, "PD 116,795," which is described as a chemically novel dopamine autoreceptor agonist, not as a D_2 antagonist. [Tr. 1261-1262 (Roth); Tr. 888 (Castagnoli)]

Defendants argue that the Wise poster presents structure-activity relationship information that would have led one of ordinary skill in the art to change OPC-4392's propoxy linker to a butoxy linker and substitute chlorine atoms for the methyl substituents at the 2 and 3 positions of the phenyl ring. As explained below, however, the actual data in the poster fail to support Defendants'

arguments. Indeed, it is undisputed that Defendants' expert, Dr. Castagnoli, misinterpreted the reported data in several critical respects.

Under the "Methods" section in the left column of the Wise poster, there is a reference to inhibition of spontaneous locomotor activity, which is abbreviated as the "LMA" test in the poster. [DTX 398] The LMA test takes advantage of the fact that when rodents are placed in a novel environment, they explore it. [Tr. 1262 (Roth)] This behavior is called "locomotor activity." [Tr. 1262 (Roth)] The LMA test measures the ability of a drug to inhibit this natural exploratory behavior in rodents. [Tr. 1262-1263 (Roth)]

Referring to the LMA test, Dr. Castagnoli testified: "If we go to the right, we have the behavioral test. And the behavioral test here tells the PHOSITA that the chloro compound is more potent in inhibiting spontaneous locomotion." [Tr. 750 (Castagnoli)] He then stated: "[I]t's my understanding that the pharmacologists interpret behavioral tests of this sort as being -- as reporting on postsynaptic D2 antagonism." [Tr. 750 (Castagnoli)] Dr. Castagnoli then testified that the LMA test measures "D2 antagonism, which translates into antipsychotic activity." [Tr. 751 (Castagnoli)] As Dr. Roth pointed out, however, Dr. Castagnoli's testimony that the LMA test measures postsynaptic D_2 antagonism was incorrect. [Tr. 1269-1271 (Roth)] Defendants do not appear to dispute that Dr. Castagnoli's understanding of the LMA test was fundamentally wrong. In fact, Defendants' expert Dr. Marshall agreed that the LMA test is not a specific test for D_2 dopamine receptor postsynaptic antagonism. [Tr. 2195 (Marshall)]

It was undisputed that the LMA test is not a specific test for D_2 dopamine receptor postsynaptic antagonism. [Tr. 1264 (Roth)] Suppression of spontaneous locomotion therefore cannot be directly associated with antipsychotic activity. [Tr. 1264-1265 (Roth); PTX 440] Many

compounds or substances that are not antipsychotics give false positive results in the LMA test including, for example, caffeine; any compound that has CNS depressant activity; general anesthetic agents; paralytic agents; ethanol; the spice nutmeg; and antidepressants such as amitriptyline, mianserin, and citalopram. [Tr. 1265-1269 (Roth); PTX 535] All of these substances are active in the LMA test, but have no antipsychotic activity. [Tr. 1265-1269 (Roth); PTX 535] Dr. Castagnoli was unaware of the numerous false positives associated with the LMA test. [Tr. 886-867 (Castagnoli)]

Schizophrenia researchers, including Dr. Roth, commonly seek to identify potential antipsychotics that are inactive in the LMA test. [Tr. 1266-1267 (Roth)] This is because, if a compound inhibits spontaneous locomotion, it "may just simply be paralyzing the mice." [Tr. 1266 (Roth)] If a drug subsequently has no effect in an antipsychotic screen (such as inhibition of amphetamine-induced locomotion), "it may simply be because the mice are paralyzed." [Tr. 1266 (Roth)] Ideally, therefore, a potential antipsychotic drug should have no effect on spontaneous locomotion, but be active in an antipsychotic screening test. [Tr. 1266-1267 (Roth)]

Dr. Castagnoli also purported to rely on certain haloperidol binding information in Table 2 of the Wise poster. Defendants failed to establish, however, that Dr. Castagnoli had ever run such a test or that he even had any understanding of the test. By contrast, it is undisputed that Dr. Roth is quite familiar with these sorts of assays because his lab performs "thousands of them in a week." [Tr. 1271 (Roth)] Dr. Roth has used this type of assay since 1979. [Tr. 1271, 1274 (Roth); DTX 398]

As Dr. Roth explained, the Wise poster does not describe a fully completed haloperidol binding experiment. [Tr. 1271 (Roth)] The Parke-Davis researchers only tested a single concentration of test compound in the haloperidol binding assay: 10^{-7} molar. [Tr. 1272 (Roth)]

Therefore, contrary to Dr. Castagnoli's erroneous testimony, one cannot infer potency of a compound based on these results. [Tr. 1272-1273 (Roth)] Rather, one would have to perform a complete dose-response study to determine the IC_{50} value and from that generate a Ki value. [Tr. 1272 (Roth)] Ki values are needed to infer potency of compounds; potency cannot be based on single-point inhibition studies. [Tr. 1271-1274 (Roth); DTX 398]

Dose-response studies test the ability of a drug to bind to a receptor at various doses or concentrations. [Tr. 1273 (Roth)] From that information one can generate a concentration-response curve or an inhibition binding curve. [Tr. 1273 (Roth)] One can then obtain the inhibition constant (Ki) of the drug, which can be compared to the Ki value of other drugs. [Tr. 1273 (Roth)] One cannot infer anything about relative drug potency based on the incomplete data presented in the Wise poster. [Tr. 1273-1274 (Roth)] Dr. Roth explained that it is axiomatic that one cannot infer relative potency based on the sort of data presented in the Wise poster. [Tr. 1273-1274 (Roth)] Defendants introduced no evidence to the contrary. There is no dispute, therefore, that Dr. Castagnoli's interpretation of the data was fundamentally flawed.

The only conclusion that one of ordinary skill in the art in October 1988 could have drawn from the haloperidol binding data in the Wise poster was that there was inhibition of binding at a single concentration of 10^{-7} molar. [Tr. 1275 (Roth)] One of ordinary skill would not have used that information to infer relative potencies of different compounds. [Tr. 1275 (Roth); DTX 398]

Dr. Castagnoli testified that his understanding was that the 10^{-7} molar figure in the Wise poster was the concentration of haloperidol used in the binding experiment. [Tr. 884 (Castagnoli)] His testimony, however, was once again factually incorrect because the 10^{-7} molar figure represented the concentration of test compound used, not the concentration of haloperidol. [Tr. 1275-1277 (Roth)]

Defendants do not appear to dispute that Dr. Castagnoli's understanding of the haloperidol binding test also was incorrect on this point. In fact, Defendants' expert Dr. Marshall again testified to the contrary of Dr. Castagnoli, explaining that the 10^{-7} molar figure represented the concentration of the test compounds. [Tr. 353 (Marshall)]

Contrary to Dr. Castagnoli's flawed analysis, a person of ordinary skill in the art in October 1988 could not have reasonably concluded that any of the coumarins disclosed in the Wise poster were antagonists at postsynaptic D_2 dopamine receptors. [Tr. 1278 (Roth)] The poster does not describe any specific test of antagonism of postsynaptic D_2 receptors. [Tr. 1278 (Roth)] Further, there would have been no scientific basis for a person of ordinary skill in the art in October 1988 to conclude that any of the coumarins of the Wise poster had reduced or no autoreceptor agonism properties and, therefore, must be potent D_2 antagonists. [Tr. 1277-1278 (Roth)] As Dr. Roth testified, "I'm unable to infer that from the data in the poster, and I don't believe anybody skilled in the art would be able to do that, either." [Tr. 1277-1278 (Roth)]

Dr. Castagnoli's testimony in this regard appears to have been based on an analysis proposed by Dr. Marshall. [Tr. 880 (Castagnoli)] On cross-examination, Dr. Marshall claimed that this interpretation was "not far-fetched" but ultimately conceded that he was unaware of any scientific publication supporting his approach to reinterpreting the Wise poster data. [Tr. 422-23, 431-32 (Marshall)]

The DOPA accumulation after GBL test described in the Wise poster is a test for autoreceptor agonism, not postsynaptic D_2 antagonism. [Tr. 1278-1279 (Roth); DTX 398] Thus, the pharmacological tests described in the Wise poster, including the LMA and GBL tests, bear no relation to the stereotypy test used by Otsuka to discover aripiprazole. Consistent with that difference

in pharmacological screening tests, there is no evidence that any of the coumarins disclosed in the Wise poster are pharmacologically similar to aripiprazole. [Tr. 1279 (Roth); DTX 398] None of Parke-Davis's coumarins, for example, including PD 116,795, ever became an FDA-approved antipsychotic drug. [Tr. 1279 (Roth); Tr. 1677 (Nichols)]

Contrary to Defendants' assertion, the Wise poster does not suggest the use of a butoxy linker in either coumarins or carbostyrils. The poster in fact identifies a propoxy-linked compound, PD 116,795, as the key and most promising antipsychotic compound, thus teaching a preference for a propoxy linker. [DTX 398] If one of ordinary skill in the art in October 1988 were relying on the Wise poster to design an antipsychotic compound, there is no reason that person would have excluded propoxy-linked compounds. [Tr. 1677-1678 (Nichols)] To the contrary, propoxy-linked compounds would have been included based on Parke-Davis's teachings in the poster, including its preferred compound, PD 116,795, which had a propoxy linker. [Tr. 1678 (Nichols)]

Moreover, Dr. Castagnoli's own testimony directly refutes Defendants' argument that the Wise poster teaches a preference for a butoxy linker. Dr. Castagnoli testified that the data in the Wise poster showed that a butoxy-linked compound (PD 119,220) was "a better presynaptic dopamine autoreceptor agonist." [Tr. 676 (Castagnoli)] He then testified that "it was the antipsychotic activity that she [the PHOSITA] wanted to enhance, not the agonist activity at the presynaptic receptor." [Tr. 754 (Castagnoli)] Dr. Castagnoli's testimony thus unequivocally established that one of ordinary skill in the art would not have selected a butoxy linker, because the data in the Wise poster established that such a structural feature led to potent autoreceptor agonism, which Dr. Castagnoli testified was undesirable in an antipsychotic.

Dr. Castagnoli's repeated errors in interpreting the data in the Wise poster also undercut his assertion that the data teach toward a 2,3-dichloro substituted antipsychotic. Moreover, the poster explicitly indicates that the tested coumarins lost all activity upon substitution of the phenyl ring, thus further teaching away from the structural features of aripiprazole, which has a disubstituted phenyl ring. [DTX 398] The abstract, for example, states that the phenylpiperazinyl group was quite sensitive to modifications and that the addition of chlorine or methyl substituents to the phenyl portion of the phenylpiperazine "resulted in complete loss of DA [dopamine] agonist activity." [Tr. 1672 (Nichols); DTX 398] The summary similarly indicates that dopamine agonist activity was sensitive to structural modifications and that a requirement for activity was "No substituents on the terminal phenyl ring." [Tr. 1672-73 (Nichols); DTX 398] Consistent with the poster's conclusion that substitution on the phenyl ring eliminated activity, Parke-Davis's exemplary coumarin (PD 116,795) had no substituents on the phenyl ring. [Tr. 1673 (Nichols)]

If a person of ordinary skill in the art in October 1988 were relying on the Wise poster to design an antipsychotic compound, there is no reason that person would have excluded unsubstituted compounds. [Tr. 1678 (Nichols)] To the contrary, unsubstituted compounds would have been included based on Parke-Davis's teachings in the Wise poster, including its preferred compound, PD 116,795, which had no substitution on the phenyl ring. [Tr. 1678 (Nichols)] Moreover, Parke-Davis "clearly stated in their summary at the end that no substitution was tolerated on this ring" and "therefore, that would teach toward an unsubstituted compound." [Tr. 1678 (Nichols)] Again, Dr. Castagnoli's erroneous interpretation of the test data provides no basis for a contrary conclusion.

No prior art suggested that any of the coumarins of the Wise poster could be modified to arrive at aripiprazole. [Tr. 1676-1677 (Nichols)] A person of ordinary skill in the art in October 1988

would not have been led toward aripiprazole based on the information in the Wise poster. [Tr. 1279 (Roth); DTX 398] It would not have been possible for a person of ordinary skill in the art in October 1988 to identify aripiprazole as a potential antipsychotic based on the information in the Wise poster. [Tr. 1676 (Nichols)] As Dr. Nichols explained: "Well, to begin with, they were looking at coumarin derivatives, not carbostyril derivatives. And they were looking for autoreceptor agonists, which is different from the action of aripiprazole. And there was no teaching that would suggest you should substitute the ring here. In fact, they clearly stated for their type of activity, no substitutions were tolerated on that phenyl ring." [Tr. 1676 (Nichols)]

2. The '456 Patent Does Not Suggest Modifying OPC-4392

Parke-Davis's coumarins are also disclosed in U.S. Patent No. 4,701,456 ("the '456 patent"). [Tr. 1679 (Nichols); DTX 629] Example 3 of the '456 patent describes a compound having a 2,3-dichloro substituted phenyl group along with several other compounds. No test data are provided for the 2,3-dichloro substituted coumarin in the '456 patent. Nothing in the '456 patent would have led a person of ordinary skill in the art in October 1988 to select the 2,3-dichloro substituted coumarin as a lead compound for antipsychotic drug discovery. [Tr. 1680-81 (Nichols)]

If a person of ordinary skill in the art in October 1988 were relying on the '456 patent to design an antipsychotic research program, there is no reason that such person would have focused on the 2,3-dichloro substituted coumarin to the exclusion of all the other coumarins identified in the patent. [Tr. 1681 (Nichols)]

The only compounds in the '456 patent that were tested for potential antipsychotic activity were propoxy-linked compounds with no substituents on the phenyl ring. [DTX 629] These features make these compounds structurally distinct from aripiprazole. Moreover, certain compounds that

were tested did not contain phenylpiperazine groups, rendering them even more structurally distinct from aripiprazole. [Tr. 893-97 (Castagnoli)] Dr. Castagnoli admitted that, if he reviewed the test data disclosed in the '456 patent, he was not sure he understood those data. [Tr. 892-93 (Castagnoli)]

The only compound specifically claimed in the '456 patent in a method for treating psychosis was a coumarin compound with a propoxy linker and no substituents on the phenyl ring, which was claimed in claim 11. [Tr. 897-900 (Castagnoli)] Thus, there is no disclosure in the '456 patent that would have led a person of ordinary skill in the art in October 1988 to select and then modify OPC-4392 to arrive at aripiprazole. [Tr. 1682 (Nichols)]

3. The Nakagawa Declaration Does Not Suggest Modifying OPC-4392

Defendants assert that the mouse jumping data in the Nakagawa declaration would have led a person of ordinary skill in the art to change OPC-4392's propoxy linker to a butoxy linker and to change its 2,3-dimethyl substituents to 2,3-dichloro substituents. Nothing in the Nakagawa declaration, however, would have led a person of ordinary skill in the art in October 1988 to select OPC-4392 as a lead compound and then modify it to arrive at aripiprazole. [Tr. 1667 (Nichols)] There was "no teaching in Nakagawa that would suggest that you should modify 4392 in any way." [Tr. 1667 (Nichols)]

One of ordinary skill in the art would not have attempted to draw any SAR conclusions from the mouse jumping data of the Nakagawa declaration because that was not the purpose of the declaration. [Tr. 1639 (Nichols)] The data, in any event, do not support Defendants' SAR arguments. Defendants argue, for example, that the data show an increase in potency in going from a propoxy-linked compound (compound 6) to a butoxy-linked compound (compound 41). Defendants introduced no evidence, however, that the ED_{50} values for these two compounds were significantly

different. The ED_{50} value (5.5 mg/kg) for the butoxy-linked compound was less than two times more potent than the ED_{50} value (9.3 mg/kg) for the propoxy-linked compound. According to the testimony of both Dr. Roth and Dr. Nichols, which Defendants never disputed, less than a two-fold difference in ED_{50} values would not be interpreted as significant. [Tr. 1323-1324 (Roth); Tr. 1644 (Nichols)] Rather, as Dr. Roth explained, because ED_{50} values are log normally distributed, a three-fold or greater change in ED_{50} values generally would be considered significant. [Tr. 1323-1324 (Roth); Tr. 1644 (Nichols)] Thus, Defendants failed to establish that one of ordinary skill in the art would interpret the mouse jumping data as suggesting any significant improvement for a butoxy-linked compound.

There is no prior art information as to the activity of OPC-4392 in the mouse jumping test. Accordingly, one of ordinary skill in the art would have had no way of knowing how the Nakagawa compounds would compare to OPC-4392 in the mouse jumping test. One of ordinary skill in the art would have considered it possible that OPC-4392 was more potent in the mouse jumping test than all of the compounds in the Nakagawa declaration. [Tr. 855 (Castagnoli)]

In his obviousness analysis, Dr. Castagnoli excluded the structural features of the most potent compound in the Nakagawa declaration. [Tr. 856 (Castagnoli)] A person of ordinary skill in the art would not have done so in attempting to create a new antipsychotic.

Dr. Castagnoli confirmed that the data in the Nakagawa declaration provided no reasonable expectation of the activity in the mouse jumping test for a compound having chlorine substituents at the 2 and 3 positions of the phenyl ring. He testified during his deposition that one of ordinary skill would have had no expectation as to whether activity in the mouse jumping test would increase or decrease if one took test compound 39 in the Nakagawa declaration, which had a single chlorine

substituent at the 3 position on the phenyl ring, and added a second chlorine at the 2 position to make it a 2,3-dichloro substituted compound. Dr. Castagnoli admitted that one of ordinary skill would have had no expectation as to the activity of the resulting 2,3-dichloro substituted compound because there were "no data available on the Jumping Test that would be relevant to such that would support such an expectation." [Tr. 864-867 (Castagnoli)] Dr. Castagnoli confirmed the accuracy of this testimony. [Tr. 867, 870-871 (Castagnoli)] He provided no contrary testimony at trial.

Otsuka incorporates by reference its remaining arguments regarding the Nakagawa declaration set forth in Section IV.E.2 above.

4. The '416 Patent Does Not Suggest Modifying OPC-4392

Defendants argue that the '416 patent would suggest making both carbostyril and dihydrocarbostyril modified versions of OPC-4392. The '416 patent, however, does not refer to OPC-4392 or any potential modification of that compound. Moreover, if a person of ordinary skill in the art were relying on the '416 patent to modify OPC-4392, there is no reason that person would have disregarded all the other structural variations described in the patent, including, for example, the numerous substituted phenyl groups described at column 4 (none of which is a 2,3-dichloro substituted group) or the structural variations reflected in the 500 exemplary compounds. [Tr. 1624-1625 (Nichols); Tr. 241 (Press); DTX 6] Otsuka incorporates by reference its remaining arguments regarding the '416 patent set forth in Section IV.F.1 above.

None of the prior art references cited by Defendants in this case disclose a compound that became an FDA-approved antipsychotic drug. [Tr. 1285 (Roth)]

The prior art cited by Defendants demonstrates that aripiprazole and OPC-4392 are quite different in their clinical and pharmacologic properties. Clinically, OPC-4392 did not treat the

positive symptoms of schizophrenia whereas aripiprazole is highly effective in treating schizophrenia. In their pharmacology they also appear to have a number of striking differences in that aripiprazole has the opposite pharmacological profile *in vivo*. [Tr. 1206 (Roth)] In the rodent pharmacology, OPC-4392 appears to have more activity as an autoreceptor agonist and little activity at postsynaptic D_2 receptors. [Tr. 1206 (Roth)] For instance, where aripiprazole is quite potent in the stereotypy test, OPC-4392 is even less potent than chlorpromazine in the stereotypy test. Chlorpromazine is the least potent antipsychotic drug. [Tr. 1317-1320 (Roth); DTX 104]

I. The 2,3-Dichloro Propoxy Compound Does Not Render Aripiprazole Obvious

Defendants raise a new obviousness defense, not identified in the pretrial order, based on the 2,3-dichloro propoxy compound disclosed in the SE '945 application and DE '105 patent. Otsuka is moving to strike this untimely raised new defense. In the event the motion is denied, Otsuka presents the following additional proposed findings of fact establishing that this defense lacks merit.

The SE '945 application is the Swedish counterpart to the '416 patent. [DTX 1159T] Like the '416 patent, the SE '945 application fails to describe the 2,3-dichloro propoxy as an antipsychotic or otherwise suggest that it would be a suitable lead compound for antipsychotic drug development. [DTX 1159T] It also fails to disclose aripiprazole. [Tr. 214-215 (Press)]

Like the '416 patent, the SE '945 application discloses dozens of carbostyril compounds. [Tr. 1690 (Nichols)] The compounds disclosed in the SE '945 application, again like the '416 patent, are said to have antihistamine action and regulating action on the central nervous system. [Tr. 215 (Press)] The SE '945 application discloses a number of therapeutic indications consistent with antihistaminic activity. [DTX 1159T at 4]

The SE '945 application further states that the compounds of the invention are useful "as means of controlling the central nervous system as muscle relaxants, sleeping agents, presurgery drugs, antischizophrenia agents, sedatives, anxiolytics, drugs for manic-depressive psychosis, fever-lowering agents, analgesics, and 'depressors.'" [DTX 1159T at 5; Tr. 1688 (Nichols)] There is no substantive difference between that sentence and the corresponding sentence in the '416 patent. A person of ordinary skill in the art in October 1988 would not have interpreted that sentence to mean that every compound disclosed in the SE '945 application would have all ten of those potential therapeutic indications. [Tr. 1688-89 (Nichols)] No compound has been approved by the FDA for all ten of those therapeutic indications. [Tr. 1689 (Nichols); Tr. 217 (Press)] For example, there is no antipsychotic agent that is used as a presurgery drug. [Tr. 217 (Press)] Nor is any antipsychotic agent used to lower fever. [Tr. 217 (Press)]

The SE '945 application provides no experimental data at all relating to potential antipsychotic activity. [Tr. 1689 (Nichols); Tr. 217-218 (Press)] There is no information in the SE '945 application that would have informed a person of ordinary skill in the art in October 1988 as to which of the specifically identified compounds, if any, would have antipsychotic activity. [Tr. 1689-90 (Nichols); Tr. 218-219 (Press)]

Dr. Press singled out a 2,3-dichloro substituted propoxy-linked compound in Example 134 of the SE '945 application; however, it is apparent that he did so only using hindsight knowledge of aripiprazole's chemical structure. [Tr. 219 (Press)] Example 134 discloses 86 different compounds, and the 2,3-dichloro propoxy compound is the twenty-second of those 86 listed compounds. [DTX 1159T] There is no suggestion in the SE '945 application that the 2,3-dichloro propoxy compound would be a better antipsychotic than any of the other listed compounds. [Tr. 1691 (Nichols); Tr. 219-

220 (Press)] If a person of ordinary skill in the art were relying on the SE '945 application in October 1988 to design a potential antipsychotic, there is no reason that person would have selected the 2,3-dichloro propoxy compound as a lead compound rather than one of the other listed compounds. [Tr. 1691 (Nichols)]

None of the compounds of the SE '945 application were ever advanced to clinical trials in humans. [Tr. 1691 (Nichols)] None of those compounds ever became an approved antipsychotic drug. [Tr. 1691 (Nichols); Tr. 220 (Press)]

A person of ordinary skill in the art in October 1988 who was not aware of aripiprazole's chemical structure could not have identified aripiprazole as a potential antipsychotic from the disclosure of the SE '945 application. [Tr. 1691-1692 (Nichols)]

The same 2,3-dichloro propoxy compound is disclosed in Example 317 of the German counterpart to the '416 patent, German Patent No. 2,912,105 ("the DE '105 patent"). [DTX 4] The disclosure of the DE '105 patent is substantially the same as the SE '945 application except that the DE '105 patent omits any mention of potential antischizophrenic activity. [DTX 4] Thus, the DE '105 patent provides even less disclosure that would have led one of ordinary skill in the art to aripiprazole.

The SE '945 application and DE '105 patent simply list the unsubstituted butoxy compound and the 2,3-dichloro propoxy compound among hundreds of other specifically named compounds. [DTX 1159T; DTX 4] They do not associate those two compounds in any way as a pair or "bracket." Nor do the SE '945 application or DE '105 patent suggest combining any structural features of those two particular compounds or provide any reasonable expectation of success of creating an improved antipsychotic drug from any such combination.

J. Objective Evidence Establishes the Nonobviousness of Aripiprazole

Defendants cannot establish a *prima facie* case of obviousness. Even if they could, there is overwhelming objective evidence of nonobviousness, including evidence of long-felt but unmet need, failures of others, commercial success, copying, unexpected results, and industry acclaim.

1. Long-felt but Unmet Need

As described above in Section III.D, as of 1988, there was a long-standing medical need for an improved antipsychotic drug that could treat the positive symptoms of schizophrenia with reduced side effects. [Tr. 1133-1134, 1144-1145, 1150-1151 (Roth); Tr. 2046-2048; 2052 (Jarosz)] All antipsychotics marketed in the United States in 1988 were first-generation antipsychotics such as haloperidol and chlorpromazine, which treated the positive symptoms of schizophrenia but still caused serious side effects such as EPS and TD. [Tr. 1143 (Roth)]

Defendants have not challenged this long-felt need for an improved antipsychotic drug. Instead, Defendants point to atypical antipsychotic compounds, including risperidone, that were discovered prior to October 1988, but marketed later, and contend these drugs met this long-felt need prior to the discovery of aripiprazole. Those compounds were not FDA approved as of October 1988 and therefore were not generally available for use by the public in October 1988. [Tr. 1143, 1134 (Roth)] The Court therefore concludes that there remained an unmet need as of October 1988.

As this Court previously found, it is "undisputed that there was a long-felt but unsolved need for a safe, atypical antipsychotic that did not cause EPS or TD from at least the 1960s until 1985 and beyond." *Janssen*, 456 F. Supp. 2d at 670. Aripiprazole met that long-felt but unmet need for a safe and effective antipsychotic with reduced side effects. [Tr. 1151-1163 (Roth); PTX 86, PTX 294; Tr. 2054-2060; PTX 357]

Alternatively, Defendants contend that the evidence of long-felt but unmet need for a safe, atypical antipsychotic in October, 1988 is not relevant to nonobviousness because of the existence of Otsuka's '416 "blocking" patent, which allegedly prevented others from addressing the long-felt need before Otsuka. Defendants have not proven, however, that the alleged blocking patent, the '416 patent, in fact blocked any others from doing research in this area.

The evidence of record also demonstrates that the '416 patent did not act to block research in this area, and, in particular, did not act to block research concerning aripiprazole. Defendant Teva filed numerous patent applications directed to crystalline forms of aripiprazole while the '416 patent was still in force. [PTX 612, 613, 620, 624, 625, 659] Defendants unsupported blocking patent theory is further addressed in Section IV.J.3 below.

2. Failures of Others

As discussed above in Section III.D, researchers attempted for years to create an improved antipsychotic that would treat the positive symptoms of schizophrenia without causing EPS, TD, or other adverse effects such as agranulocytosis. Those efforts largely failed, as reflected, for example, by the fact that the FDA did not approve a single new antipsychotic drug from about 1976 to 1989. [PTX 319; PTX 320; PTX 321; PTX 322; Tr. 1565-1585, 1588 (Nichols); PTX 113-123; PTX 125-131; PTX 133-170; PTX 175; PTX 179-183; PTX 220; PTX 227-228; PTX 245; PTX 282-286; Tr. 1134-1136 (Roth); Tr. 1565 (Nichols); PTX 79] *See also Janssen*, 456 F. Supp. 2d at 670 (finding that there was a failure to develop a safe atypical antipsychotic). These widespread failures further establish that aripiprazole would not have been obvious.

3. Commercial Success

Abilify® has also achieved a great deal of commercial success, and that commercial success is directly tied to the invention of the '528 patent. [Tr. 2081-2082 (Jarosz)]

There is no dispute that there is a relationship between the invention of the '528 patent and the successful commercial product, Abilify® . [PTX 1; Tr. 2003 (Jarosz)] The asserted claims of the '528 patent cover the molecule that is known as aripiprazole, chemical compositions that include aripiprazole, and methods to use aripiprazole in the treatment of schizophrenia in a patient. [PTX 1; Tr. 2003 (Jarosz)] Aripiprazole is the active ingredient in the pharmaceutical product currently available in the United States under the trade name of Abilify® , which product is sold in the United States by Otsuka and its marketing partner, Bristol Myers Squibb ("BMS") . [Tr. 2003-04 (Jarosz)] Thus, there is a clear nexus between the '528 patent claims and the commercial product Abilify® .

Abilify® also has been enormously successful. Even before Abilify® had ever received FDA approval, BMS recognized the value of the '528 patent and was optimistic enough about aripiprazole that they were willing to invest $157 million upfront and another $60 million in milestone payments to Otsuka for rights to the product. [Tr. 2011-13 (Jarosz); PTX 354] As Mr. Jarosz explained, the $157 million up-front payment made from BMS to Otsuka for rights to Abilify® was quite substantial as compared to other payments that BMS has been involved with related to other pharmaceutical products over the years. It exceeded all but two payments that BMS has been a part of from 1999 to 2008. [PTX 354; PTX 362-370; Tr. 2013-15 (Jarosz)] Morever, by 2009, seven years after Abilify® had been on the market, BMS had had enough opportunity to observe the success of Abilify® that they were willing to pay another $400 million to continue the collaboration agreement for the life of the '528 patent. [Tr. 2012-13 (Jarosz); PTX 356] This is evidence of the recognition by BMS of the substantial value of Otsuka's '528 patent.

Commercial sales of Abilify® also have been substantial and have steadily grown since launch. Starting in 2002, when Abilify® was first approved in the United States, sales were $38.1 million. [PTX 347-348; PTX 385; PTX 775; Tr. 2020-21 (Jarosz)] By the end of 2009, sales of Abilify® were $3.3 billion on an annual basis. [PTX 775; Tr. 2020-21 (Jarosz)] The total U.S. sales of Abilify® by Otsuka and BMS, through all distribution channels, have been $12.5 billion from its introduction in November of 2002 through February of 2010. [PTX 775; Tr. 2022 (Jarosz)] From 2005 onward, sales of Abilify® exceeded a billion dollars each year, qualifying it as a "blockbuster drug." [PTX 372; PTX 775; Tr. 2021 (Jarosz)]

Abilify® also has been widely prescribed. Total prescriptions of Abilify® have steadily grown since its introduction in 2002. [PTX 352; PTX 353; PTX 387; PTX 388; Tr. 2029-2030 (Jarosz)] In 2007, IMS data show that total prescriptions written for Abilify® totaled 5.5 million, including all different dosage forms. [PTX 352; PTX 353; Tr. 2027-29 (Jarosz)] In 2003, the refill rate for Abilify® prescriptions was about 33 percent. [PTX 352; PTX 353; Tr. 2079 (Jarosz)] Since 2003, the refill rate for Abilify® has been fairly consistently in the range of 40 to 45 percent. [PTX 352; PTX 353; Tr. 2079 (Jarosz)] This refill rate demonstrates that customers who have used Abilify® tend to continue using Abilify® at a high rate. [Tr. 2079 (Jarosz)] This is presumably due to the many benefits that flow from the patented molecule, aripiprazole. [Tr. 2079 (Jarosz)]

Abilify® also has been extremely successful when compared to the other products in its relevant market. [Tr. 2029-34, 2037-39 (Jarosz); PTX 349 - PTX 353; PTX 373] Abilify® largely competes in the marketplace with other atypical antipsychotics and, to a lesser extent, with some of the older-generation, typical antipsychotics. [PTX 386 - PTX 388; Tr. 2008 (Jarosz)] In its first 12 months, Abilify® generated revenues, after adjusting for inflation, of $331 million. [PTX 775; Tr.

2029 (Jarosz)] Those sales exceeded the first-year sales of each of the other atypical antipsychotics to date, except one. [Tr. 2029 (Jarosz); PTX 350] Despite being the sixth atypical antipsychotic to enter the market, as of the second quarter of 2008, Abilify® had climbed to become the third most successful atypical antipsychotic in terms of total prescriptions written. [PTX 352 and PTX 353; Tr. 2029-30 (Jarosz)]

In 2009, Abilify® was the second largest selling atypical antipsychotic, behind only Seroquel, and the sixth most successful prescription drug in the United States (as measured in dollar sales). [PTX 776 and PTX 777; Tr. 2032 (Jarosz)] Abilify® is also one of the most successful products introduced in the industry in the last few years, when compared to the quarterly sales performance of other compounds that were launched. [PTX 374; Tr. 2038 (Jarosz)] When compared to other top pharmaceutical product launches, including the launches of Advair, Avandia, Celebrex, Lipitor, Nexium, Rezulin, Viagra, Vioxx, and Zyprexa, Abilify® is in the top seven product launches in industry history. [PTX 781; Tr. 2039 (Jarosz)] Abilify® has been BMS's second largest blockbuster drug to date. [PTX 782; Tr. 2037-2038 (Jarosz)]

Mr. Jarosz further explained that the benefits and advantages of the '528 patent have been the primary drivers of Abilify®'s commercial success, not other factors such as marketing or pricing. The types of marketing undertaken for Abilify® are common and similar to those for other pharmaceutical products. [Tr. 2072 (Jarosz)] Abilify®'s advertising and promotion to sales ratio, including expenditures on sales force, fell within the typical range for the rest of the pharmaceutical industry. [Tr. 2073 (Jarosz)] Moreover, advertising and marketing for Abilify® has focused on communicating the unique efficacy and side effect profiles of the patented drug molecule. [Tr. 2063-70 (Jarosz)]

Thus, this advertising and marketing was directly tied to the benefits and advantages of the '528 patent.

Abilify® has also been priced comparably to or at a premium compared with other atypical antipsychotics. [Tr. 2080 (Jarosz)] Therefore Abilify® 's commercial success could not have been due to a price advantage over other atypical drugs. Abilify®'s success was due instead to the advantages associated with the aripiprazole molecule. [PTX 357; Tr. 2080 (Jarosz)]

In short, (1) the commercial product, Abilify® , is a direct product manifestation of the '528 patented invention; (2) Abilify® has attained a high level of commercial success, both in terms of absolute numbers, as well as compared to other products within the relevant market; and (3) the advantages and benefits of the '528 patent, including the unique pharmacological profile and clinical advantages of the aripiprazole molecule, have been the significant driver of that commercial success. [Tr. 2081-2082 (Jarosz)] Thus, the substantial commercial success of Abilify® supports the nonobviousness of the '528 patent.

a. Defendants Have Failed to Rebut the Showing of Commercial Success

Defendants do not contest the enormous commercial success of Abilify® . Defendants contend instead that the commercial success of aripiprazole is not relevant to nonobviousness because of the existence of Otsuka's '416 "blocking" patent, which allegedly prevented others from discovering and profiting from aripiprazole before Otsuka. Defendants have not proven, however, that the alleged blocking patent, the '416 patent, in fact blocked any others from doing research in this area. Defendants have presented no evidence that any competitor ever refrained from developing aripiprazole or other carbostyril derivatives due to concerns about any "blocking" patent owned by

Otsuka. Defendants also have no expert testimony to support this speculative theory and instead rely on unsupported anecdotes and attorney argument.

Defendants rely primarily on Dr. Press's testimony about his experiences researching clozapine derivatives. This testimony has no bearing on whether the '416 patent blocked work concerning structurally distinct carbostyril compounds and Dr. Press declined to testify as to that specific issue:

> Q. Can you identify any company or researcher who actually refrained from performing research on carbostyril derivatives based on concerns about Otsuka's '416 patent?
>
> A. I think, as we talked about earlier, I'm not privy to what's gone on in the various pharmaceutical companies within their proprietary walls, so I'm not in a position to be able to answer your question.

[Tr. 307 (Press)] In response to the Court's further question on this matter, Dr. Press also readily disclaimed any ability to generally opine on what legal and business decisions companies might have made in light of the '416 patent: "that question you ask has business decision concerns and also really has legal concerns that – I really am not in a position to be able to answer your question very well." [Tr. 174-75 (Press)] Defendants also cite to Dr. Nichols's testimony, but Dr. Nichols did not offer any opinion that the '416 patent acted as a blocking patent, and specifically disclaimed the legal expertise to opine in this area. [Tr. 1712-13 (Nichols)] This testimony therefore does not support Defendants' argument that the '416 patent acted as a "blocking" patent.

The evidence of record also demonstrates that the '416 patent did not block research in this area, and, in particular, did not act to block research concerning aripiprazole. Defendant Teva filed numerous patent applications directed to crystalline forms of aripiprazole while the '416 patent was

still in force. [PTX 612, 613, 620, 624, 625, 659] This evidence directly contradicts Defendants' blocking patent argument.

Defendants point out that these patent applications were not filed until after aripiprazole was approved by the FDA in November 2002. This argument, however, is beside the point. Either the '416 patent in fact blocked research in this area or it did not. Defendants' patenting activity indicates it did not, and Defendants have not identified any specific evidence to the contrary.

Finally, Defendants point to other factors they contend negate Abilify®'s commercial success. Defendants improperly point to the fact that Otsuka and BMS paid fines to the Department of Justice and District of Massachusetts in settlement of claims that Otsuka and BMS improperly marketed Abilify®. Defendants do not explain why such settlements affect either the commercial success of Abilify® or the nexus between the commercial success of Abilify® and the '528 patent. Likewise, Defendants point to the '416 patent and contend that some of Abilify®'s commercial success must be due to this patent. Defendants make no effort, however, to quantify how the '416 patent might detract from Abilify®'s commercial success, nor do they contend that it affects the nexus between Abilify®'s success and the '528 patent claims. Nor do Defendants explain how the '416 patent can be responsible for the commercial success of a product based on a compound that is not disclosed in the '416 patent. The Court therefore rejects this unexplained and unsubstantiated argument.

As such, Otsuka demonstrated the substantial commercial success of Abilify®, and Defendants have failed to rebut the evidence of that commercial success or the nexus of that success to the benefits and advantages of the '528 patent.

4. Copying

All seven generic drug companies in these consolidated litigations have filed ANDAs directed to aripiprazole tablets. Each of these companies seeks to market exact generic copies of aripiprazole, the compound covered by claims 12, 17 and 23 of the '528 patent. All actively participating Defendants have stipulated to infringement of these asserted claims and their copying of aripiprazole in their ANDAs is evidence of nonobviousness. *See Janssen*, 456 F. Supp. 2d at 671 (finding that copying of antipsychotic drug risperidone by generic drug company ANDA filers was evidence of nonobviousness).

Defendants also have copied aripiprazole in the filing of their own patent applications relating to aripiprazole. Teva has conducted research on crystalline forms of aripiprazole and methods of their preparation, and sought patent protection. [*See* PTX 612 and PTX 620] Teva has additionally pursued patent protection on the processes it has developed for preparing aripiprazole and an intermediate in the synthesis of aripiprazole. [*See* PTX 613, PTX 624, and PTX 625] Other entities have similarly conducted research, and sought patent protection, on different polymorphs of aripiprazole, processes for their preparation, and pharmaceutical compositions containing them and their use. [*See* PTX 659]

In these patent filings Defendants further directly copied the teachings of the '528 patent. For example, one of Teva's U.S. Patent Applications directly copied portions of the text of the '528 patent, paraphrased additional language, and failed to cite to the '528 patent as the source document for any of this language. [Compare PTX 612 at page 1 [0003] with PTX 1 at col. 1, lines 15-50] One of Teva's scientists, Dr. Ben-Zion Dolitzky, further testified during his deposition that he read the '528 patent to learn how Otsuka had synthesized aripiprazole. [Dolitzky Trans. 169:12 -176:13] Dr. Dolitzky then used this information in his own scientific work as indicated by his patent, which cites

to the '528 patent in multiple places and explains that "U.S. Pat. No. 5,006,528 discloses a process for the preparation of aripiprazole." [PTX 613 at page 1 [0006]] Dr. Dolitzky's patent further incorporates the entire subject matter of the '528 patent by reference. [PTX 613 at page 1 [0011]]

The Court concludes that Otsuka has demonstrated extensive copying of the subject matter of claims 12, 17 and 23 of the '528 patent.

5. Unexpected Results

a. Unique and Unexpected Benefits of Aripiprazole

Aripiprazole has a number of unexpected therapeutic benefits as a partial dopamine agonist, including its broad efficacy in treating the positive symptoms of schizophrenia and favorable side-effect profile, e.g., causing reduced or no EPS, TD, sedation, weight gain or other metabolic effects, prolactin elevation, or orthostatic hypotension. [Tr. 1151-1163 (Roth); PTX 86, PTX 294; Tr. 2054-2060; PTX 357] Defendants introduced no evidence that the drug's therapeutic benefits and side-effect profile could have been predicted in 1988. [Tr. 1060 (Roth); Tr. 1591 (Nichols)]

Aripiprazole has been approved for the treatment of schizophrenia in both adults and pediatric patients 10 to 17 years of age. [DTX 564] In addition, aripiprazole has been approved for several other indications, including as an add-on treatment for major depressive disorders [DTX 564], for acute treatment of adults with manic or mixed episodes associated with Bipolar I Disorder [DTX 564], for the acute treatment of pediatric patients 10 to 17 years of age with manic or mixed episodes associated with Bipolar I Disorder [DTX 564], for maintenance treatment of Bipolar I Disorder [DTX 564], for the acute treatment of agitation associated with schizophrenia or Bipolar I Disorder [DTX 564], and for the treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years of age. [Tr. 1360-61 (Roth); 2062 (Jarosz); PTX 372; DTX 564] Defendants introduced no

evidence that aripiprazole's efficacy in treating those medical conditions would have been known or expected to a person of ordinary skill in 1988.

Defendants contend that Otsuka has not proven that the multiple therapeutic benefits for aripiprazole constitute unexpected results because Otsuka did not show that the various other prior art carbostyril compounds did not have these properties. The Court is unconvinced by this argument. Given the unrebutted testimony concerning the complexity and challenges of antipsychotic drug discovery, Otsuka has provided ample evidence that the various therapeutic benefits of aripiprazole would have been unexpected.

b. Unexpected Superiority in Animal Testing

Aripiprazole exhibits unexpectedly favorable test results in an animal test model for potential antipsychotic activity and also for cardiovascular side effects associated with antipsychotic medications. Aripiprazole exhibits unexpectedly strong potency in the stereotypy test, indicating antipsychotic efficacy, while simultaneously exhibiting low potency in the anti-epinephrine lethality test, indicating a low potential to cause cardiovascular side effects. [Tr. 1094-1095, 1099-1100, 1120 (Roth); Tr. 1956-1967 (Hirose)] These favorable animal model test results were completely unpredictable from the prior art. [Tr. 1098-1100 (Roth); Tr. 1959 (Hirose)]

For example, aripiprazole exhibited unexpectedly greater potency in the stereotypy test than each of the specific prior art carbostyril derivatives that Defendants have identified as lead compounds in their obviousness analysis. Data reported in an article published by Otsuka in 1998 showed that the unsubstituted butoxy compound (compound no. 4) was inactive in the stereotypy test up to the highest dosage tested. [Tr. 1229-32; 1239-40 (Roth); PTX 564 at 661] This same article also reported that OPC-4392 (compound no. 1) showed very low potency in the stereotypy test,

consistent with Dr. Oshiro's observations during his research leading to the discovery of aripiprazole that OPC-4392 showed low potency in this test and therefore was ineffective in treating the positive symptoms of schizophrenia. [PTX 564 at 661; Tr.1754; 1768-69 (Oshiro)]

As for the third lead compound identified by Defendants, the 2,3-dichloro substituted propoxy compound, this compound was tested and directly compared to aripiprazole in Dr. Hirose's declaration, which showed that aripiprazole was superior to it.

(1) The Hirose Declaration Demonstrated Aripiprazole's Superior Properties as Compared to the Prior Art

During the reexamination of the '528 patent, Otsuka submitted the Hirose declaration to the PTO to demonstrate the unexpectedly superior properties of the claimed compounds for treating schizophrenia with fewer side effects, as compared to the most structurally similar compounds shown in the applied references as determined by the Examiner. [PTX 20]

The Hirose declaration reports test results using two preclinical screening tests: the inhibition of apomorphine-induced stereotypical behavior test in mice ("the stereotypy test") and the inhibition of epinephrine-induced lethality test in mice ("the anti-epinephrine lethality test"). [Tr. 1071-1071 (Roth); PTX 20]

(a) The Stereotypy Test

The stereotypy test measures the ability of a drug to attenuate or block postsynaptic D_2 dopamine receptor signaling and therefore is used to predict the *in vivo* potency and efficacy of antipsychotic drugs. [Tr. 1071 (Roth)] All known effective antipsychotic drugs that are approved by the FDA share the property of blocking or attenuating postsynaptic D_2 dopamine receptor signaling. [Tr. 1074 (Roth)] All effective FDA-approved antipsychotic drugs can inhibit

apomorphine-induced stereotypy. [Tr. 1075-1076 (Roth)] This is true for both typical and atypical antipsychotic drugs. [Tr. 1075-1076 (Roth)]

The stereotypy test was the first screening test that Dr. Oshiro and his colleagues at Otsuka used to identify aripiprazole as a potential antipsychotic drug. [Tr. 1751-1756 (Oshiro)] Otsuka was correct in predicting that aripiprazole would be an antipsychotic based on its potency in the stereotypy test. [Tr. 1087 (Roth)]

The stereotypy test also has been widely used by others to evaluate potential anti-psychotic drugs. [Tr. 1074-1075 (Roth)] Many pharmaceutical companies used the stereotypy test to screen for potential antipsychotic drugs in the 1980s, including in 1988. [Tr. 1074-1075 (Roth)] Pharmaceutical companies are still using the stereotypy test today to screen for potential antipsychotic drugs. [Tr. 1075 (Roth)]

The stereotypy test is discussed as a test for potential antipsychotic activity in a large number of peer-reviewed scientific publications and patents. [Tr. 1076-1084 (Roth); PTX 305; PTX 450; PTX 456; PTX 442; PTX 433]

Dr. Roth provided a detailed explanation at trial as to how the stereotypy test is performed. [Tr. 1071-1072 (Roth)] To perform the stereotypy test, initially a test drug is given to the mouse, then some period of time later apomorphine is given. [Tr. 1071 (Roth)] Apomorphine is a dopamine agonist that activates postsynaptic D_2 dopamine receptors and thereby induces stereotypical behaviors in mice. [Tr. 1071-1072 (Roth)] The stereotyped behaviors include head movements, sniffing, licking, and gnawing. [Tr. 1073 (Roth)] The degree of stereotyped behavior is assessed based on a rating scale. [Tr. 1071 (Roth)] Multiple doses of the test drug are administered to different mice and an estimate of potency of the drug is subsequently calculated from the data. [Tr. 1071 (Roth)] The

potency is calculated in the form of an ED_{50} value. [Tr. 1072 (Roth)] Lower ED_{50} values are more favorable in the stereotypy test because they represent greater drug potencies. [Tr. 1071-1072 (Roth)]

Dr. Roth further described the specific procedures and blinding methodology used by Otsuka scientists Dr. Hirose and Dr. Kikuchi in performing the stereotypy testing reported in the Hirose declaration. [Tr. 1103-1108 (Roth)] Dr. Roth presented a step by step explanation of how these scientists conducted the comparison of aripiprazole versus prior art compound A, the 2,3-dichloro substituted propoxy compound. [Tr. 1103-1108 (Roth)] For the stereotypy testing of aripiprazole, in step one, Dr. Kikuchi prepared six solutions of varying concentrations of aripiprazole and then labeled the vials with a code to blind Dr. Hirose from knowing the concentration of aripiprazole in each vial. [Tr. 1103-1104 (Roth); PTX 20 and PTX 487-T] Dr. Hirose was thus blinded to dose. [Tr. 1104 (Roth); PTX 20 and PTX 487-T] Dr. Hirose then administered one oral dose of an unknown quantity of aripiprazole or placebo (control) to each of six mice. [Tr. 1104 (Roth); PTX 20 and PTX 487-T] One hour later, Dr. Hirose injected 1.5 mg/kg of apomorphine to the mice to induce stereotyped behaviors. [Tr. 1104 (Roth); PTX 20 and PTX 487-T] Dr. Hirose then rated each mouse at 20 minutes, 30 minutes, and 40 minutes after administration of apomorphine using a rating scale to measure the level of stereotypy. [Tr. 1104 (Roth); PTX 20 and PTX 487-T] The rating scale was "anchored" at 0 and 3. [Tr. 1104 (Roth); PTX 20 and PTX 487-T] A score of 0 meant no stereotypy; a score of 1 meant slight stereotyped head movements and intermittent sniffing; a score of 2 meant intense head movements and mild licking interspersed with sniffing; and a score of 3 meant intense licking and/or gnawing. [Tr. 1104-1105 (Roth); PTX 20 and PTX 487-T] Each mouse was observed for one minute before a rating was assigned and recorded on a score sheet. [Tr. 1105-1106 (Roth); PTX 20 and PTX 487-T] The experiment was then repeated five more times using a total of 36 mice.

[Tr. 1105 (Roth); PTX 20 and PTX 487-T] After completion of the test, Dr. Kikuchi broke the code and revealed the quantity of aripiprazole (or placebo) for each of the vials. [Tr. 1106-1107 (Roth); PTX 20 and PTX 487-T] From these data, Dr. Hirose and Dr. Kikuchi calculated a dose-response curve and then an ED_{50} value for aripiprazole. [Tr. 1107 (Roth); PTX 20 and PTX 487-T]

For the testing of prior art compound A, Dr. Hirose and Dr. Kikuchi switched roles. [Tr. 1107-1108 (Roth); PTX 20 and PTX 487-T] Dr. Hirose prepared the six solutions of varying concentrations of compound A for Dr. Kikuchi to test. [Tr. 1107-1108 (Roth); PTX 20 and PTX 487-T] He labeled each vial with a code to blind Dr. Kikuchi from knowing the concentration of compound A in each vial. [Tr. 1107-1108 (Roth); PTX 20 and PTX 487-T] Dr. Kikuchi then administered one oral dose of an unknown quantity of compound A or placebo (control) to each of six mice. [Tr. 1107-1108 (Roth); PTX 20 and PTX 487-T] One hour later, Dr. Kikuchi injected each mouse with 1.5 mg/kg of apomorphine. [Tr. 1107-1108 (Roth); PTX 20 and PTX 487-T] Dr. Kikuchi then observed each mouse at 20 minutes, 30 minutes, and 40 minutes after administration of apomorphine and assigned a stereotypy rating score of 0-3. [Tr. 1107-1108 (Roth); PTX 20 and PTX 487-T] Each mouse was observed for one minute before a rating was assigned. The experiment was then repeated five more times using a total of 36 mice. [Tr. 1107-1108 (Roth); PTX 20 and PTX 487-T] After completion of the test, Dr. Hirose broke the code and revealed the quantity of compound A (or placebo) for each of the vials. [Tr. 1107-1108 (Roth); PTX 20 and PTX 487-T] From these data, Dr. Hirose and Dr. Kikuchi calculated a dose-response curve and then an ED_{50} value for compound A. [Tr. 1107-1108 (Roth); PTX 20 and PTX 487-T]

Dr. Roth testified that this specific test methodology was "very ingenuous," and that "it's a marvelous way to do the experiment." [Tr. 1106; 1108 (Roth)] Dr. Roth further explained that the

observational scoring method used to collect the stereotypy data has "been extraordinarily useful." [Tr. 1117 (Roth)]

Scoring of the stereotypy test involves assigning scores to observed mouse behavior, but as Dr. Roth and Dr. Hirose each explained, the stereotypy scale used to record the stereotypy observations is not a subjective scoring method. [Tr. 1116 (Roth)] The scoring on this scale is in fact determined by specific well-defined behaviors. [Tr. 1116)] The scale reads as follows:

Score 0: Absence of stereotypy or any abnormal movement
1: Slight stereotyped head movements and intermittent sniffing
2: Intense head movements and mild licking interspersed with sniffing
3: Intense licking and/or gnawing

[Tr. 1935 (Hirose); PTX 20 at OPC0001665] Thus, a score of 0 indicates an absence of any stereotyped behavior. [PTX 20 at OPC0001665] A score of 1 requires stereotyped head movements and intermittent sniffing. [PTX 20 at OPC0001665] A score of 2 requires the appearance of licking behavior that does not appear at the lower scores of 1 or 0. [PTX 20 at OPC0001665] Finally, a score of 3 involves intense licking and/or gnawing and the absence of the sniffing behavior seen in the lower score 2. [PTX 20 at OPC0001665] Accordingly, each score on this scale defines specific behaviors that are distinct from those of the other scores. [PTX 20 at OPC0001665] Therefore, this method is objectively well-defined.[2] [Tr. 1116-1117 (Roth); 1937-38 (Hirose)]

[2] Defendants contended, relying on Dr. Beninger's testimony, that the stereotypy scale is a subjective scoring method. Dr. Beninger, focused only on certain behaviors in the stereotypy scale, however, and did not consider the fact that the specific combinations of behaviors are unique for each scoring level. Accordingly, the Court rejects this testimony.

(b) The Anti-Epinephrine Lethality Test

In addition to the stereotypy test, Dr. Hirose used the anti-epinephrine lethality test to demonstrate the superior therapeutic profile of the claimed compounds over the prior art. The anti-epinephrine lethality test measures blockade of alpha-1 adrenergic receptors and thereby predicts a compound's propensity to induce orthostatic hypotension in humans. [Tr. 1088-1089 (Roth)]

Cardiovascular side effects are quite significant in people with schizophrenia. Orthostatic hypotension, for example, can cause an individual to faint from a sudden drop in blood pressure when they stand up. [Tr. 1090 (Roth)] The individual may fall and sustain a concussion or a subdural hematoma, which is potentially fatal. [Tr. 1090 (Roth)] In elderly patients, orthostatic hypotension is a common cause of broken hips, which leads to increased morbidity and mortality. There are other cardiovascular side effects induced by alpha-1 blockade. [Tr. 1090 (Roth)]

Prior to the Hirose declaration, the anti-epinephrine lethality test, along with the stereotypy test, was used by Dr. Oshiro in the '528 patent to demonstrate the superiority of the claimed compounds as potential antipsychotics. [Tr. 1090 (Roth); PTX 1] The data are summarized in Table 3 at column 16 of the patent. [Tr. 1090 (Roth); PTX 1] The last column of Table 3 provides "(B)/(A)" ratios for each compound, where (B)/(A) is the ratio of activity in the anti-epinephrine lethality test to that in the stereotypy test. [Tr. 1090 (Roth); PTX 1] This ratio is known as the "therapeutic index" or "protective ratio" and is calculated by dividing a compound's ED_{50} value in the anti-epinephrine lethality test by its ED_{50} value in the stereotypy test. [Tr. 1090 (Roth); PTX 1] The ratio is a relative index of the ability of a drug to potentially treat schizophrenia versus its propensity to induce side effects related to alpha-1 blockade. [Tr. 1090 (Roth); PTX 1] The higher

the ratio, the safer the antipsychotic drug. [Tr. 1090 (Roth); PTX 1] The therapeutic index is useful in comparing potential antipsychotic drugs. [Tr. 1091-1092 (Roth); PTX 1]

Dr. Roth also explained in detail how to perform the anti-epinephrine lethality test. [Tr. 1088-1089 (Roth)] A test compound is first given to a mouse and then a dose of epinephrine is administered that, in the absence of the test compound, would reliably kill one-hundred percent of the mice. [Tr. 1088 (Roth)] The effect of that particular dose of test compound is estimated based on the number of surviving mice. [Tr. 1088 (Roth)] Various doses of the test compound are given, and, from this, one can obtain an ED_{50} value for the inhibition of epinephrine-induced lethality in mice. [Tr. 1089 (Roth)] Unlike the stereotypy test, a higher value is desired in the anti-epinephrine lethality test. [Tr. 1089 (Roth)]

(c) The Hirose Declaration Test Results

Dr. Roth and Dr. Hirose each testified concerning the test results reported in the Hirose declaration. That testimony was not challenged by Defendants who did not present any testimony concerning the actual test results reported in the Hirose declaration, aside from their criticism of the test methods addressed below.

The claimed compounds that were evaluated in the stereotypy and anti-epinephrine lethality tests in the Hirose Declaration were designated test compound Nos. 1, 5, 6 and 8. [Tr. 1092-1094 (Roth); PTX 20] The chemical structures of those compounds were shown on page 3 of the declaration. [Tr. 1092-1094 (Roth); PTX 20] Test compound 1 was aripiprazole. [Tr. 1092 (Roth); Tr. 1968-1969 (Hirose); PTX 20] These claimed compounds were compared to prior art compounds designated A, B, C, and D. [Tr. 1092-1094 (Roth); PTX 20] The chemical structures of the prior art compounds A, B, C, and D were shown on pages 4 and 5 of the Hirose declaration. [Tr. 1092-1093

(Roth); PTX 20] Compound A is the 2,3-dichloro substituted propoxy-linked compound. [Tr. 1093 (Roth); PTX 20]

As both Dr. Roth and Dr. Hirose explained, the reported test results showed the superiority of aripiprazole as compared to the 2,3-dichloro substituted propoxy-linked compound. [Tr. 1094-1100 (Roth); Tr. 1956-1957 (Hirose)] The ED_{50} value for aripiprazole in the stereotypy test was 0.28 mg/kg and the ED_{50} value for aripiprazole in the anti-epinephrine lethality test was greater than 128 mg/kg. [Tr. 1094 (Roth); Tr. 1954-55 (Hirose); PTX 20] Dr. Roth calculated a B-over-A ratio for aripiprazole as greater than 457. [Tr. 1321 (Roth)] The ED_{50} value for prior art compound A in the stereotypy test was 6.47 mg/kg and the ED_{50} value for compound A in the anti-epinephrine lethality test was greater than 128 mg/kg. [Tr. 1095 (Roth); Tr. 1956 (Hirose); PTX 20] Dr. Roth calculated a B-over-A ratio for compound A of greater than 19.8. [Tr. 1095 (Roth)] Accordingly, aripiprazole was 23-fold more potent in the stereotypy test than compound A and aripiprazole's B-over-A ratio was also 23-times higher than the B-over-A ratio for compound A. [Tr. 1095-1096 (Roth)]

Dr. Roth and Dr. Hirose also explained that the Hirose declaration data showed the superiority of the remaining three claimed compounds compared to the prior art compounds. [Tr. 1096-97 (Roth); 1954-57 (Hirose)] Compound 5 was 10-fold more potent in the stereotypy test than compound B. Dr. Roth calculated the B-over-A ratio for compound 5 as greater than 251 and the B-over-A ratio for compound B as 10.6. [Tr. 1096 (Roth); PTX 20] The B-over-A ratio for compound 5 was thus 24-fold higher than the B-over-A ratio for compound B. [Tr. 1096 (Roth); PTX 20] Compound 6 was 14-fold more potent in the stereotypy test compared to compound C. [Tr. 1097 (Roth); PTX 20] Dr. Roth calculated the B-over-A ratio for compound 6 as 21.4 and the B-over-A ratio for compound C as 0.2. [Tr. 1097 (Roth); PTX 20] The B-over-A ratio for compound 6 was

thus 107-fold higher than the B-over-A ratio for compound C. [Tr. 1097 (Roth); PTX 20] Compound 8 was 7-fold more potent in the stereotypy test compared to compound D. [Tr. 1097 (Roth); PTX 20] Dr. Roth calculated the B-over-A ratio for compound 8 as 24 and the B-over-A ratio for compound D as 3. [Tr. 1097 (Roth); PTX 20] The B-over-A ratio for compound 8 was thus 8-fold higher than the B-over-A ratio for compound D. [Tr. 1097 (Roth); PX 20]

Therefore, the overall range of increased potency in the stereotypy test for compounds 1, 5, 6, and 8 of the '528 patent compared to prior art compounds A through D was 7- to 23-fold more potent. [Tr. 1098 (Roth); PTX 20] Those differences were pharmacologically substantial. A 7- to 23-fold increase in inhibiting stereotypy would not have been expected or predictable to a person of ordinary skill in the art in October 1988. [Tr. 1098 (Roth); Tr. 1958-59 (Hirose)]

With respect to the B-over-A ratios, the overall results showed that compounds 1, 5, 6, and 8 of the '528 patent had 8- to 107-fold more favorable B-over-A ratios compared to the prior art compounds. [Tr. 1098 (Roth); PTX 20] Those differences in B-over-A ratios were substantial. [Tr. 1099 (Roth)] An 8- to 107-fold increase in B-over-A ratios would not have been expected or predictable to a person of ordinary skill in the art in October 1988. [Tr. 1098-1099 (Roth)]

These differences in B-over-A ratios meant that the claimed compounds were likely to be associated with fewer of the cardiovascular side effects associated with alpha-1 receptor blockade, including orthostatic hypotension and tachycardia. [Tr. 1099-1100 (Roth)] Tachycardia is another serious cardiovascular side effect and can lead to an arrhythmia. [Tr. 1100 (Roth)] That reduced propensity to cause orthostatic hypotension or other cardiovascular side effects would not have been expected or predictable to a person of ordinary skill in the art in October 1988. [Tr. 1099-1100 (Roth); Tr. 1959 (Hirose)]

(2) Defendants Have Not Shown Any Problems with the Design and Conduct of the Hirose Study

Defendants did not present at trial any testing of their own to rebut Otsuka's testing of aripiprazole and other compounds as reported in the Hirose declaration and Dr. Oshiro's 1998 article. Defendants also did not dispute Otsuka's interpretation of this test data. Defendants instead criticize the design and conduct of the stereotypy testing presented in the Hirose declaration, alleging that the stereotypy data are unreliable because the testing methods used to obtain the data were "susceptible to confound and bias." Defendants further contend that simple changes to the study design could have cured these alleged problems.

Defendants have not identified any facts in support of these speculative arguments of bias and confounding. Nor have they presented any detailed analysis of the study design or test results. Defendants presented their criticisms of Dr. Hirose's declaration at trial through the testimony of a single witness, Dr. Beninger. Dr. Beninger did not conduct any stereotypy testing of his own, despite his stated concerns about the Hirose data. [Tr. 959 (Beninger)] Nor did he attempt to recalculate Dr. Hirose's test results. [*Id.*] Moreover, while Dr. Beninger criticized the stereotypy scoring procedures used in generating the data reported in the Hirose declaration, including the use of an allegedly subjecting scoring scale, it was shown on cross examination that Dr. Beninger has published stereotypy test results using similar scoring scales. [Tr. 986-88 (Beninger)]

Otsuka's experts Dr. Roth and Dr. Thisted independently analyzed the stereotypy data presented in Dr. Hirose's declaration, repeated the reported calculations, and concluded that the results were valid and that there is no evidence of bias or confounding. [Tr. 1108-1116 and 1124-1125 (Roth); Tr. 1488 (Thisted)] Dr. Hirose also testified that the study design used for the stereotypy

testing was a standard study design used by Otsuka and was not susceptible to the bias and confounding alleged by Dr. Beninger. [Tr. 1931 and 1938-1939 (Hirose)] Defendants have failed to show any problems with the design of the stereotypy experiments presented in the Hirose declaration.

(a) Dr. Roth's and Dr. Thisted's Confirmation of the Hirose Stereotypy Study Test Results

In addition to his detailed analysis of how Dr. Hirose and Dr. Kikuchi conducted the stereotypy testing reported in the Hirose declaration, Dr. Roth also described how he independently confirmed the test results reported in the Hirose declaration. [Tr. 1125, 1306-1308 (Roth)] Dr. Roth reviewed the raw data and recalculated the dose-response curves used to generate the ED_{50} values reported in the declaration, concluding that there were no problems with the data. [Tr. 1125, 1306-08 (Roth); PTX 487T]

Dr. Thisted, an expert biostatistician with many years of experience in analyzing study design, additionally presented his analysis of the methodology and calculations used to obtain the stereotypy data presented in the Hirose declaration. [Tr. 1437-1439 (Thisted)] As Dr. Thisted explained, for each compound tested, Dr. Hirose obtained stereotypy scores for each of multiple doses of the test compound, as well as a dose of zero milligrams per kilogram (the control dose). [Tr. 1446 (Thisted)] These test data were used to compute a dose-response curve, using standard procedures. [Tr. 1450-1452 (Thisted)] The dose-response curves were then used to compute ED_{50} values, which were reported in the Hirose declaration. [Tr. 1448 (Thisted)]

Dr. Thisted independently recalculated these dose-response curves, using the same raw data used by Dr. Hirose [PTX 487; PTX 487T], and further independently calculated ED_{50} values for each

of the compounds tested in the Hirose declaration. [Tr. 1450 (Thisted); PTX 557] In each case, Dr. Thisted obtained ED_{50} values that were the same as those reported in the Hirose declaration to the number of decimal places reported there, with one exception, in which Dr. Thisted's calculation and Hirose's calculation differed by one unit in the last decimal place, an insubstantial difference. [Tr. 1452 (Thisted); PTX 487T, PTX 557] Accordingly, Dr. Thisted confirmed Dr. Hirose's calculations of the ED_{50} values reported in his declaration. [Tr. 1450-52 (Thisted); PTX 557]

Dr. Thisted further considered the differences in the ED_{50} values for the claimed compounds versus the prior art compounds. [Tr. 1455-1456 (Thisted); PTX 557] His calculations demonstrated that each of the comparisons reported in the Hirose declaration represents a statistically significant difference in ED_{50} values, in each case with the claimed compound having the lower ED_{50}. [Tr. 1455-56 (Thisted); PTX 557] Accordingly, Dr. Thisted confirmed that Dr. Hirose's conclusions concerning the superior potency of the claimed compounds in the stereotypy test as compared to the prior art compounds were well-supported by the data. [Tr. 1455-1456 (Thisted); PTX 20 and PTX 557]

(b) Defendants' Allegations of Confounding

Defendants did not challenge Dr. Roth's and Dr. Thisted's confirmation of the Hirose study results. Instead, Defendants criticized the study design. Dr. Beninger first criticized the fact that two observers were used to collect the stereotypy data. For each comparison between a claimed and prior art compound, one observer (Dr. Hirose or Dr. Kikuchi) would collect data for the claimed compound, while the other would collect data for the comparison compound. Dr. Beninger alleged that this study design resulted in a confound, because it was impossible to tell whether the differences in the stereotypy test results between the claimed and comparison compounds were due to differences between the claimed and comparison compounds or merely due to differences in the way the

observers measured the stereotypy scores. [Tr. 931 (Beninger)] Dr. Roth, Dr. Thisted, and Dr. Hirose each testified in response to these allegations.

Dr. Roth testified that there was nothing inappropriate about having two investigators perform this type of behavioral screening test. The use of two investigators reduces the amount of rater fatigue. [Tr. 1101-1102 (Roth)] It is quite common to have multiple trained raters perform this sort of study. [Tr. 1101 (Roth)] Dr. Roth, for example, commonly uses two investigators when his lab performs these type of behavioral studies. [Tr. 1101 (Roth)]

Dr. Roth further explained that his analysis of the data, including the dose-response curves, did not reveal any indication of the type of confounding alleged by Dr. Beninger. [Tr. 1109-1110 (Roth)] Dr. Roth reviewed the raw data and dose-response curves for the stereotypy testing reported in the Hirose declaration and concluded that there was a "high degree of correlation between the two raters," Dr. Hirose and Dr. Kikuchi. [Tr. 1112 (Roth)] The degree of stereotypy observed by each rater when the mice were given a control (zero) dose of active compound was quite similar for the two raters. [Tr. 1111-1112 (Roth)] In Dr. Roth's experience, there are practical reasons why the data would show good inter-rater reliability. [Tr. 1112-1113 (Roth)] The more senior investigator (Dr. Kikuchi) trained the more junior investigator (Dr. Hirose) in stereotypy rating. [Tr. 1112-1113 (Roth)] In addition, they routinely performed stereotypy testing in their drug discovery program. For these reasons, one would expect a high degree of interrater reliability. [Tr. 1112-13 (Roth)].

In addition, based on the dose-response curves, there was no evidence of any systematic error or skewing of the data that would indicate any confound. [Tr. 1109-1110 (Roth)] Dr. Roth found the raw data to be "of high quality" and the dose-response curves to be what he would expect from trained raters. [Tr. 1110 (Roth)] Dr. Roth's analysis of the raw data agreed with a statistical analysis

of the data performed by Dr. Thisted. [Tr. 1113 (Roth); PTX 487T] The Court finds Dr. Roth's testimony persuasive, as he routinely analyzes this sort of data in his lab "every day." [Tr. 1109-1112 (Roth)].

Dr. Thisted similarly explained that the study design and test results did not support Dr. Beninger's allegation of confounding. [Tr. 1468-1470 and 1482-1486 (Thisted] Dr. Thisted explained that the overall study incorporated a feature that statisticians call balance, which ensured that each of the investigators evaluated two of the claimed compounds and two of the prior art comparison compounds. [Tr. 1468-1470 and 1482 (Thisted)] This aspect of the study design eliminated the possibility of confounding in the Hirose studies. [Tr. 1469 (Thisted)] If the differences observed in the comparisons were due to the fact that Dr. Hirose evaluated the test mice differently than Dr. Kikuchi, those differences would not tend to favor either the claimed or prior art comparison compounds, because Dr. Hirose and Dr. Kikuchi each tested two of the four claimed compounds and two of the four prior art compounds. [Tr. 1468-69, 1482 (Thisted)]

Dr. Thisted further explained how he performed a statistical analysis of the raw data to determine if there was any evidence that Dr. Hirose evaluated mice differently than Dr. Kikuchi. [Tr. 1482-1485 (Thisted); PTX 557] In doing so, Dr. Thisted looked at the control mice from all of the studies (the mice that received no drug at all). [Tr. 1482-1483 (Thisted)] Because the control mice received no drug, if there were differences in the way the two investigators used the stereotypy scale, those differences should be apparent in their evaluation of the control mice. [Tr. 1482-1483 (Thisted)] Dr. Thisted therefore looked at stereotypy data for the control mice evaluated by Dr. Kikuchi and compared those data to the stereotypy data for the control mice evaluated by Dr. Hirose. [Tr. 1483 (Thisted)] A statistical comparison of those data revealed essentially no difference between

Dr. Kikuchi's and Dr. Hirose's evaluation of the control mice. [Tr. 1483 (Thisted); PTX 557] Accordingly, Dr. Thisted concluded that there was no difference in how Dr. Kikuchi and Dr. Hirose were applying the stereotypy scale and therefore no evidence to support Dr. Beninger's allegation of confounding. [1483-1486 (Thisted); PTX 557]

Dr. Beninger did not address the balanced study design discussed by Dr. Thisted, nor did he conduct any statistical calculations to assess potential bias or otherwise respond to Dr. Thisted's calculations. [Tr. 959 (Beninger)] Dr. Beninger simply contended that Dr. Thisted's calculations were unconvincing because they only analyzed the control mice which, in Dr. Beninger's view, exhibited the maximum amount of stereotypy. [Tr. 946 (Beninger)] As Dr. Thisted explained, however, Dr. Beninger's criticism of his statistical analysis is incorrect. [Tr. 1487 (Thisted)] In fact, each of the control groups included mice that exhibited less than the maximum stereotyped behavior, including mice exhibiting behavior scored with values of 1 and 2 on the stereotypy scale, and not just the maximum score of 3. [Tr. 1465-1466 and 1487 (Thisted)] As a result, analysis of the control mice provides information on how the observers assigned scores of 1, 2 and 3 on the stereotypy scale, not just the maximum score of 3. [Tr. 1465-1466 and 1487 (Thisted)]

Dr. Hirose also testified concerning Dr. Beninger's allegations of confounding. [Tr. 1937-1940 (Hirose)] Dr. Hirose explained that he and Dr. Kikuchi had worked together in analyzing stereotyped behaviors in experiments for a long time, beginning in 1987. [Tr. 1938-1939 (Hirose)] Based on this experience, Dr. Hirose testified there should be no difference in how he and Dr. Kikuchi apply the stereotypy scale. [Tr. 1938-1939 (Hirose)]

The Court is persuaded by the testimony and detailed analysis presented by Dr. Roth, Dr. Thisted, and Dr. Hirose and concludes that Defendants have not established any "confounding" of the Hirose stereotypy data.

(c) Defendants' Allegations of Bias

Dr. Beninger additionally criticized the Hirose study design because the scientists who conducted the stereotypy experiments reported in the Hirose declaration were aware of the identity of the compounds being tested. Dr. Beninger opined that, having knowledge of the identify of the test compounds, the observers might be inclined to "shade" their observations of stereotyped behaviors to favor the claimed compounds over the prior art compounds. [Tr. 1946-1947 (Beninger)] Otsuka's witnesses, Dr. Roth, Dr. Thisted, and Dr. Hirose again convincingly testified in response that the stereotypy data reported in the Hirose declaration were not biased as alleged by Dr. Beninger. [Tr. 1113-1116; 1124-1125 (Roth); Tr. 1456-1463 (Thisted)]

Dr. Roth explained that he reviewed the Hirose stereotypy data and saw no evidence of the type of bias alleged by Dr. Beninger. (Tr. 1115 (Roth)] Dr. Roth testified that the type of blinding employed by Dr. Hirose, wherein the observer was blinded to the identity of the specific doses administered to the mice, but not the identity of the compound administered to the mice, was sufficient. [Tr. 1113-1114 (Roth)] Given the fact that the doses were all randomized and blinded, any bias would be readily apparent from the dose-response curves, which would be skewed. [Tr. 1114-1115 (Roth)] That is not the case here. To the contrary, as Dr. Roth testified, the dose-response curves were "perfectly fine" and "regular." [Tr. 1115, 1124-1125 (Roth)] He saw nothing unusual in the dose-response curves. [Tr. 1115 (Roth)] There is no evidence of any systematic bias in the underlying data. [Tr. 1113-1116; 1124-1125 (Roth)].

Dr. Thisted similarly testified that he saw no evidence of any biasing of the Hirose test data. [Tr. 1456-1463 (Thisted)] Dr. Thisted explained that the stereotypy study was designed in such a way that it incorporated important elements of experimental design that guarded against the kind of bias that Dr. Beninger suggests. [Tr. 1456-1463 (Thisted)] Those elements are that the observer was blinded to the specific dose of test compounds administered to any individual test mouse and the mice are tested in random order relative to the dosage being tested. [Tr. 1456-1460 (Thisted)] Accordingly, when the observer is making the individual observations of the test mice, he does not know the dosage of compound administered. [Tr. 1459-1460 (Thisted)] Given this study design, Dr. Thisted explained that it is impossible for the observer to bias the study results, because he does not know for any individual mouse how he should bias the results to result in a more favorable ED_{50} value. (Tr. 1458-1460 (Thisted)] To generate a viable dose-response curve, mice administered zero doses or low doses should show little effect due to the test compound, while mice administered the highest doses should show the maximum effect. [Tr. 1458-1460 (Thisted)] Thus, an observer seeking to bias the test results would want to bias the observed drug effect in different directions depending on the dosage administered. [Tr. 1458-1460 (Thisted)] The observer, however, was unaware of those individual dosages. [Tr. 1460 (Thisted)] Dr. Thisted therefore concluded that this blinding as to dosage administered was sufficient to prevent any conscious or subconscious biasing of the data. [Tr. 1458-60 (Thisted)]

Dr. Thisted further identified another aspect of the test design that specifically addressed the type of biasing suggested by Dr. Beninger. [Tr. 1462-1463 (Thisted)] Dr. Beninger testified that it would be possible to systematically shade all of the evaluations for a specific compound, at all doses tested, shading them either up or down to favor the claimed compound over the prior art compound.

[Tr. 1462-1463 (Thisted)] As Dr. Thisted explained, however, in computing the dose-response curve, the data were normalized so as to guard against that type of bias. [Tr. 1462-1463 (Thisted)] In this normalization process, results for the stereotypy measurements at each of the doses tested were divided by the stereotypy measurement for the mice that were not administered any of the test compound, the control mice. [Tr. 1462-1463 (Thisted)] Because systematic shading of the data would be present for all mice tested, including the control mice, this normalization of the test data would tend to cancel out any such alleged shading of the data. [Tr. 1463 (Thisted)] Dr. Thisted therefore concluded that the study design guarded against the possible biasing suggested by Dr. Beninger. [Tr. 1463 (Thisted)]

Dr. Thisted additionally performed a statistical analysis of the raw data underlying the stereotypy test results reported in the Hirose declaration to determine whether there was any evidence of the type of bias suggested by Dr. Beninger. [Tr. 1464-1465 (Thisted); PTX 557] Dr. Thisted looked at the control mice from all of the studies, the mice that received no drug at all of any sort. [Tr. 1464-1465 (Thisted); PTX 557] Dr. Thisted compared the stereotypy scores for control mice in the studies concerning the claimed compounds with those in the studies from the comparative drugs, and saw no difference in how the control mice were scored. [Tr. 1465 (Thisted); PTX 557] The average stereotypy scores were essentially the same for the control mice in the studies involving the claimed compounds and the comparison compounds. [Tr. 1465 (Thisted); PTX 557] Dr. Thisted's statistical analysis of these data indicated that there was no statistically significant difference in how the stereotypy scales were being used in the control mice between claimed studies and comparative studies. [Tr. 1465 (Thisted); PTX 557] Accordingly, the data did not reveal any evidence of the sort of bias suggested by Dr. Beninger. [Tr. 1464-65 (Thisted); PTX 557]

Dr. Beninger did not address the elements of the stereotypy study design discussed by Dr. Roth and Dr. Thisted, nor did he provide any statistical analysis of the study data as presented by Dr. Thisted. In response to Dr. Thisted's statistical analysis, Dr. Beninger contended that this analysis was unconvincing because Dr. Thisted only analyzed control mice and therefore only investigated possible bias for mice exhibiting the maximum amount of stereotyped behavior. [Tr. 943-944 (Beninger)] Again, Dr. Thisted explained that Dr. Beninger's criticism of his statistical analysis was incorrect. [Tr. 1465-1466 (Thisted)] The control groups included mice that exhibited less than the maximum stereotyped behavior, and as a result, analysis of the control mice provides information on mice exhibiting varying degrees of stereotyped behavior. [Tr. 1466 (Thisted)] This analysis revealed no evidence of any bias. [Tr. 1465-66 (Thisted); PTX 557]

Dr. Hirose also testified concerning Dr. Beninger's allegations of bias. [Tr. 1931 (Hirose)] Similar to Dr. Roth and Dr. Thisted, Dr. Hirose testified that the blinding methodology employed in the stereotypy testing underlying his declaration, whereby the observer was blinded to the identity of the dosage of the compound being tested, eliminated the possibility of any biasing of the test results. [Tr. 1931 (Hirose)]

The Court is persuaded by the testimony and detailed analysis presented by Dr. Roth, Dr. Thisted, and Dr. Hirose and concludes that Defendants have not shown that the Hirose stereotypy data exhibited any bias.

(d) Defendants' Proposed Modifications to Dr. Hirose's Stereotypy Studies

Dr. Beninger further contended that the possibility for bias and confounding that he identified could have been easily avoided by altering the study design. Dr. Beninger proposed that the observers could have been blinded to the identities of the compounds being tested and each observer could have rated half of the mice from each dose group for each compound. [Tr. 956-957 (Beninger)] Dr. Roth and Dr. Thisted each testified that these proposed modifications were unnecessary, because the stereotypy experiments did not allow for or exhibit the bias and confounding suggested by Dr. Beninger. [Tr. 1108-9, 1113-14 (Roth); Tr. 1466-68, 1487-88 (Thisted)]

Dr. Thisted further explained that Dr. Beninger's proposed modifications would have introduced a substantial level of complexity into the way the study was conducted, requiring the use of at least one other person to conduct these studies. [Tr. 1466-1467 and 1487-1488 (Thisted)] This additional complexity could introduce additional errors and variability, which would affect the precision of the ultimate assessments. [Tr. 1467-1468 and 1487-1488 (Thisted)] That scientific cost would be incurred to guard against a problem that did not exist, because, according to Dr. Thisted's analysis, the study was already designed to guard against bias and confounding. [Tr. 1467-1468, 1487-1488 (Thisted)]

Considering all of the foregoing, the Court finds, as the PTO did, that the Hirose declaration demonstrated unexpected results because the claimed compounds, including aripiprazole, were shown to have a greater potential for being effective in treating schizophrenia with fewer cardiovascular side effects caused by alpha-1 receptor blockade compared to the prior art compounds. [Tr. 1120 (Roth)]

(3) Defendants Have Not Shown That the Test Results in the Hirose Declaration Were Predictable

Defendants argue, in the alternative, that, if the Hirose declaration test results are accurate, they are predictable and therefore do not show unexpected results. Defendants' arguments for the predictability of the Hirose test results focus on the stereotypy test data. Defendants do not consider or address the predictability of the experimental results for aripiprazole in the anti-epinephrine lethality test or aripiprazole's superior therapeutic index as compared to the prior art. Accordingly, Defendants have, at best, asserted an incomplete argument for the predictability of the aripiprazole test data reported in the Hirose declaration.

Defendants present two arguments in support of their argument that the Hirose stereotypy test results were predictable. Defendants argue that internal Otsuka test data show that aripiprazole is only six-times more potent in the stereotypy test than the 2,3-dichloro substituted propoxy compound and that Dr. Oshiro testified that a six-fold difference is not unexpected. [Def. FOFCOL at 55-56] Defendants further argue that the mouse jumping test data in the Nakagawa declaration suggest the superiority of aripiprazole in the stereotypy test. [Def. FOFCOL at 56]

Defendants' first argument, that internal Otsuka test data indicate less favorable test results for aripiprazole as compared to the 2,3-dichloro substituted propoxy compound, was raised for the first time late in the trial proceedings, during the cross-examination of Dr. Oshiro. Because this argument was raised so late during trial, the internal Otsuka test data and any alleged inconsistencies with the Hirose data were not addressed by any of the parties' expert witnesses. For example, no evidence was presented concerning the test conditions underlying the internal Otsuka test data or

whether these test data may be validly compared with the Hirose test data. Absent any such evidence, the Court declines to conduct its own analysis and comparison of the data.

The only testimony relating to these test data in any way was that of Dr. Oshiro, and Dr. Oshiro was never asked whether these data could be compared to the Hirose data or whether they contradict the Hirose test results in any way. [Tr. 1900-1903 (Oshiro)]

Defendants nevertheless contend that Dr. Oshiro testified that a six-fold difference in potency, such as shown in these internal test results, would not be unexpected. Dr. Oshiro's actual testimony, however, does not support any such conclusion. Defendants rely on Dr. Oshiro's testimony concerning test results for OPC-4392 and a compound created by replacing the propoxy linker group in OPC-4392 with a butoxy linker group. Dr. Oshiro testified that this structural modification to OPC-4392 did not result in the same "15-fold activity increase" he had seen when he had made a similar structural modification to his "seed compound," OPC-4310:

> A: As I indicated earlier, when the propoxy in 4310 was changed to butoxy, such as in 14542, the activity increased 15-fold. And so we wanted to confirm as to whether or not the OPC-4392 which was undergoing clinical testing would have the same activity increase, which is the 15-fold activity increase, if the propoxy was changed to butoxy. So we decided to synthesize the compound.
>
> Q: And what did you find?
>
> A: We did not find a considerable increase in the activity such as when we saw from 4310 to OPC-14542. In other words, even if the propoxy was changed to butoxy, we did not see a surprising increase, such as the 15-fold increase.

[Tr. 1772-73 (Oshiro)]

Defendants argue that Dr. Oshiro testified here that a six-fold difference in stereotypy test results is not surprising, because test data reported in later monthly reports showed six-fold difference in the stereotypy test results for OPC-4392 versus the butoxy-linked analog. Dr. Oshiro's testimony

does not support that interpretation. Dr. Oshiro merely stated that the test data for OPC-4392 and its butoxy analog did not show the same fifteen-fold increase that he saw when he modified OPC-4310. [Tr. 1772-1773 (Oshiro)] Dr. Oshiro did not make any general statement about a six-fold increase in activity in the stereotypy test as Defendants contend. [Tr. 1772-1773 (Oshiro)] Dr. Oshiro was never asked to identify the stereotypy test data for OPC-4392 and its butoxy analog he had in mind when he offered this testimony, and it is unclear whether Dr. Oshiro recalled the specific details of those test results. [Tr. 1772-1773 (Oshiro)] To the extent Dr. Oshiro did recall specific test results for OPC-4392 and its butoxy analog, it is also unclear whether he was referring to the same test data cited by Defendants, because Defendants never asked. [Tr. 1772-1773 (Oshiro)]

At most, Defendants have merely pointed to Otsuka internal test data showing that aripiprazole, in one test, was found to be six times more potent than the 2,3-dichloro substituted propoxy compound. Given the absence of any meaningful testimony or evidence concerning these test data, the Court declines to find that this test data detracts from the strong showing of unexpected results reported in the Hirose declaration.

Defendants' second argument for the predictability of the Hirose stereotypy data is that these data are predictable in light of the mouse jumping test results reported in the Nakagawa declaration, allegedly showing the superiority of a butoxy linker group. The Nakagawa declaration, however, does not include testing of any of the compounds tested in the Hirose declaration. It was further undisputed by the parties that the mouse jumping data disclosed in the Nakagawa declaration are different from the stereotypy test data disclosed in the Hirose declaration. [Tr. 1244-45 (Roth)] Accordingly, the Nakagawa mouse jumping data cannot be directly compared with the data reported in the Hirose declaration.

Defendants also did not establish any relationship between the mouse jumping test data and the stereotypy test data and, in fact, there is no scientific correlation between results in one test with the other. [Tr. 1247-48 (Roth)] Defendants' expert Dr. Marshall offered speculative testimony that test results in these two tests may be correlated, but conceded on cross-examination that he never actually attempted any such correlation. [Tr. 2203 (Marshall)] Defendants further argued that test results in the mouse jumping test and the stereotypy test may be correlated because results in these tests each relate to anti-schizophrenic efficacy. The evidence introduced at trial established, however, that these two tests are not equivalent in this regard. [Tr. 1247-1248 (Roth)] Defendants contend that the unsubstituted butoxy compound displays excellent test results in the mouse jumping test. As noted above, however, this same compound is virtually inactive in the stereotypy test, indicating that the allegedly "excellent" mouse jumping data do not predict excellent results in the stereotypy test. [Tr. 1239-40 (Roth)] Moreover, while the stereotypy test has been widely used in antipsychotic drug development, there is no evidence that the mouse jumping test has ever been used to develop a new antipsychotic drug. [Tr. 1243-44 (Roth); Tr. 253 (Press); Tr. 851-2 (Castagnoli)]

The Nakagawa test data were also insufficient to support the conclusions that Defendants seek to draw from those data. The purpose of the data presented in the Nakagawa declaration was to show a difference in activity of the claimed compounds as compared to prior art compounds which were inactive in the mouse jumping test at the highest dose tested. [Tr. 1638-39 (Nichols); Tr. 255-256 (Press)] The data were not intended to show differences among the claimed compounds, including the unsubstituted propoxy and unsubstituted butoxy compounds, and the data were insufficient to establish any such differences for the reasons discussed above in Section IV.H.3.

6. Industry Acclaim

Abilify® has also received wide acclaim from others in the industry. In 2004, Frost & Sullivan awarded its Product Innovation Award for the U.S. antipsychotic medications market to Otsuka for Abilify® . [PTX 357; Tr. 2040-2042 (Jarosz] The award was described as being "bestowed on the company that successfully develops and commercializes a medication which is believed to provide a unique set of benefits over existing products in the market." [PTX 357; Tr. 2042 (Jarosz)] In its report covering the award, Frost and Sullivan stated: "With a comparable efficacy and superior side effect profile, Abilify® may become the new standard against which all new antipsychotics are judged." [PTX 357; Tr. 2044 (Jarosz)]

Abilify® has won a number of other awards throughout the world over the years. Among those awards, Abilify® won the prestigious Prix Galien award in 2006 (France) for being the most innovative pharmaceutical product on the market, the Pharmaceutical Executive Magazine Central Nervous System Compound of the Year for 2004 (US), and a variety of other awards in Germany, Japan, France and Spain. [PTX 375; Tr. 2042-2044 (Jarosz)] Each of these awards is evidence of the acclaim that aripiprazole has received in the industry.

K. The '528 Patent Provides Adequate Support for the Claimed Invention

Defendants raise a contingent argument, which they never sought to prove at trial, that claims 12, 17, and 23 of the '528 patent are invalid for lack of utility under 35 U.S.C. §§ 101/112 because the disclosure in the specification of the '528 patent allegedly is not adequate to support the use of aripiprazole as an antipsychotic. This argument is fatally flawed.

Claim 12 is directed to the compound aripiprazole. [PTX 1] Claim12 is not limited to any particular use of that compound and therefore Otsuka could satisfy the utility requirement of

sections 101 and 112 by disclosing any practical utility for aripiprazole, including any pharmacological activity. Here, the specification of the '528 patent discloses that aripiprazole and the other compounds of the invention have the pharmacological activity of blocking neurotransmission at dopamine receptors in the brain. [PTX 1] That disclosure of anti-dopaminergic pharmacological activity satisfies the utility requirement with respect to claim 12.

Claim 17 of the '528 patent is directed to a pharmaceutical composition containing aripiprazole for treating schizophrenia, and claim 23 is directed to a method of treating schizophrenia by administering a pharmaceutical composition containing aripiprazole. [PTX 1] The specific utility required by those claims—treatment of schizophrenia using aripiprazole—is repeatedly disclosed in the specification of the '528 patent. [PTX 1]

A person of ordinary skill in the art in 1988 would have known how to use aripiprazole as an antipsychotic for the treatment of schizophrenia based on the disclosure of the '528 patent. No undue experimentation would have been required for a person of ordinary skill to use aripiprazole to treat schizophrenia as described in the '528 patent.

In addition, the specification of the '528 patent provides stereotypy test results in mice for aripiprazole, which persons skilled in the art would understand reasonably predict antipsychotic activity in humans suffering from the positive symptoms of schizophrenia. [PTX 1]

Because Defendants performed no tests themselves, they have no basis to challenge the accuracy of the stereotypy test results presented in the specification. Aripiprazole is in fact highly potent in the stereotypy test as reported in the specification of the '528 patent and as further confirmed by extensive subsequent testing of the compound. [PTX 86, PTX 292; Tr. 1159-1161 (Roth)] Defendants cannot dispute that aripiprazole is highly potent in the stereotypy test. [Tr. 1239-1240

(Roth)] Further, Defendants admit that the "anti-apomorphine stereotypy test . . . in the '528 patent . . . correlates to antipsychotic activity." [Def. FOFCOL, page 14] Aripiprazole is indisputably useful to treat schizophrenia exactly as predicted by the stereotypy test. [PTX 86, PTX 292; Tr. 1087, and 1159-1161 (Roth)] Indeed, it has been approved by the FDA as an antipsychotic drug (Abilify®) for the treatment of schizophrenia, and Defendants are seeking to market generic copies of Otsuka's Abilify® product specifically for the treatment of schizophrenia. Defendants cannot credibly maintain that aripiprazole is not useful to treat schizophrenia. The specification of the '528 patent correctly indicates that it is useful for that purpose based on its potency in the stereotypy test. [PTX 1] No more is required to satisfy the requirements of sections 101 and 112.

Defendants' infringement of the asserted claims of the '528 patent and copying of aripiprazole, and the commercial success of aripiprazole, further establish the utility of the claimed invention and preclude Defendants' arguments to the contrary.

V. FINDINGS OF FACT RELATING TO DEFENDANTS' UNENFORCEABILITY DEFENSE

Defendants present four arguments in support of their unenforceability defense. Defendants argue allegedly inconsistent stereotypy data was withheld from the PTO, that the Nakagawa declaration was withheld from the PTO, that Otsuka's representatives presented false arguments during the reexamination of the '528 patent, and that Dr. Hirose falsely described the testing procedures underlying his declaration. Defendants offered little trial testimony or evidence in support of these arguments, and for the following reasons Defendants have failed to prove the factual allegations for any of the arguments underlying their unenforceability defense. [3]

[3] Defendants offered a constantly-shifting list of inequitable conduct arguments through the course of this litigation. In their initial Pretrial Order submitted to Honorable Magistrate Judge

A. There Was No Withholding of Any Allegedly Inconsistent Stereotypy Data

Defendants' first argument[4] in support of their unenforceability defense is that Otsuka withheld allegedly contradictory stereotypy test data concerning the 2,3-dichloro substituted propoxy linked compound. This argument was not included in the inequitable conduct arguments listed in Defendants' Pretrial Order as required by this Court, and was not raised by Defendants until late in the trial, during the cross-examination of Dr. Oshiro. In entering the parties' Pretrial Order, this Court specifically ordered that no changes to the Pretrial Order would be permitted absent a showing of "manifest injustice." [D.I. 328 (Pretrial Order) at 70] Because Defendants have not made any such showing concerning this belated argument, the Court rejects this argument.

Even if the Court were to consider this argument, however, for the following reasons, Defendants have not established any withholding of inconsistent stereotypy test data.

1. The Internal Stereotypy Data Do Not Contradict the Hirose Test Data

Defendants argue that internal Otsuka test data, showing that aripiprazole is allegedly six-times more potent than the 2,3-dichloro substituted propoxy compound in the anti-apomorphine stereotypy test, is allegedly inconsistent with the data in the Hirose declaration, which shows that

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Goodman on May 24, 2010 (*see* Ninth Pretrial Scheduling Order, D.I. 309 at ¶ 5), Defendants outlined at least eight distinct theories of inequitable conduct. [Defendants' May 24, 2010 Pretrial Order submission at pages 110-122)] In their revised Pretrial Order submitted to Honorable Magistrate Judge Goodman on June 25, 2010 [*see* Scheduling Order issued June 11, 2010, D.I. 312 at page 1], Defendants narrowed their list to focus on three theories. [Final (proposed) Pretrial Order, June 25, 2010, D.I. 328 at pages 125-131] In their Post-Trial submissions, Defendants present as their main argument, an argument they had never previously raised in the Pretrial Order or in the pleadings in these litigations. Defendants' shifting positions and belated introduction of their lead inequitable conduct argument highlights the weakness of this defense.

[4] Defendants present these arguments in different orders in different portions of their Proposed Findings. The Court relies on the order of arguments presented in Defendants' Proposed Conclusions of Law.

aripiprazole is twenty-three times more potent in this same comparison. Because Defendants did not raise this argument until late in the trial proceedings, the internal Otsuka test data and any alleged inconsistencies with the Hirose data were not addressed by any of the parties' expert witnesses. Accordingly, Defendants did not present any evidence concerning whether these two sets of test results are in fact inconsistent in any way. For example, no evidence was presented concerning the test conditions underlying the internal Otsuka test data or whether these test data may be validly compared with the Hirose test data. Absent any such evidence, the Court declines to conduct its own analysis and comparison of the data.

The only testimony relating to these test data in any way was that of Dr. Oshiro, and Dr. Oshiro was never asked whether these data contradict the Hirose test results in any way. Defendants contend that Dr. Oshiro testified that a six-fold difference in potency, such as shown in these internal test results, would not be unexpected. Dr. Oshiro's actual testimony, however, does not support any such conclusion.

Defendants rely on Dr. Oshiro's testimony concerning test results for OPC-4392 and a compound created by replacing the propoxy linker group in OPC-4392 with a butoxy linker group. Dr. Oshiro testified that this structural modification to OPC-4392 did not result in the same "15-fold activity increase" he had seen when he had made a similar structural modification to his "seed compound," OPC-4310:

> A: As I indicated earlier, when the propoxy in 4310 was changed to butoxy, such as in 14542, the activity increased 15-fold. And so we wanted to confirm as to whether or not the OPC-4392 which was undergoing clinical testing would have the same activity increase, which is the 15-fold activity increase, if the propoxy was changed to butoxy. So we decided to synthesize the compound.

Q: And what did you find?

A: We did not find a considerable increase in the activity such as when we saw from 4310 to OPC-14542. In other words, even if the propoxy was changed to butoxy, we did not see a surprising increase, such as the 15-fold increase.

[Tr. 1772-73 (Oshiro)]

Defendants argue that Dr. Oshiro testified here that a six-fold difference in stereotypy test results is not surprising, because test data reported in later monthly reports showed a six-fold difference in the stereotypy test results for OPC-4392 versus the butoxy-linked analog. Dr. Oshiro's actual testimony, however, does not support that interpretation. Dr. Oshiro merely stated that the test data for OPC-4392 and its butoxy analog did not show the same fifteen-fold increase that he saw when he modified OPC-4310. As is apparent from Dr. Oshiro's actual testimony, Dr. Oshiro did not make any general statement about a six-fold increase in activity in the stereotypy test as Defendants contend. Dr. Oshiro was never asked to identify the stereotypy test data for OPC-4392 and its butoxy analog that he had in mind when he offered this testimony, and it is unclear whether Dr. Oshiro recalled the specific details of those test results. To the extent Dr. Oshiro did recall specific test results for OPC-4392 and its butoxy analog, it is also unclear whether he was referring to the same test data cited by Defendants, because Defendants never asked.

Defendants never asked Dr. Oshiro his opinion concerning a six-fold increase in stereotypy test data and further never asked Dr. Oshiro if the internal Otsuka test data were inconsistent with the test data reported in the Hirose declaration. Defendants cannot now attempt to construct what answers Dr. Oshiro might have provided in response to these questions Defendants never posed, and Dr. Oshiro's testimony does not support the conclusions Defendants seek to draw.

2. There Is No Evidence That the Internal Stereotypy Data Were Withheld from the PTO with an Intent to Deceive

Defendants also have not established that any individual knowingly withheld this allegedly inconsistent data with an intent to deceive. Defendants allege that Dr. Oshiro was aware of the contents of the Hirose declaration and therefore must have intentionally withheld the allegedly contradictory internal data with an intent to deceive the PTO. Dr. Oshiro did not affirmatively testify, however, that he was aware of the test data submitted in the Hirose declaration. He merely testified that "most likely this draft – draft of this declaration was sent to me as an attachment to an e-mail requiring or requesting me to check the wording for the way things are worded in this document." [Tr. 1897 (Oshiro)] This testimony, reflecting Dr. Oshiro's uncertain memory in this regard, does not establish that Dr. Oshiro was aware of the specific details of the test data reported in the Hirose declaration. Because Defendants have not shown that Dr. Oshiro was aware of the specific data in the Hirose declaration, they cannot prove that he was aware of any contradiction.

Defendants also failed to offer any evidence concerning additional details underlying their allegation that Dr. Oshiro knowingly withheld contradictory test data. Defendants never inquired as to whether Dr. Oshiro recalled in 2005 the specific stereotypy test data Defendants cite. That data was generated in 1987, 18 years earlier, and was among dozens of test results reported in Dr. Oshiro's notebooks. [DTX 59T] It is therefore not apparent that in 2005 Dr. Oshiro would have recalled the details of the 1987 data.

Defendants also never inquired as to whether Dr. Oshiro believed there was any contradiction between the Hirose data and the internal stereotypy data Defendants cite. On their face, data showing a six-fold improvement and data showing a twenty-three-fold improvement are not contradictory, and

Defendants have not presented any evidence that Dr. Oshiro believed to the contrary even had he been aware of these data.

Finally, Defendants suggest Dr. Hirose may have been aware of the allegedly contradictory test data because he generated test data for aripiprazole in 1987. This does not prove that Dr. Hirose was aware of the specific data Defendants cite, and Dr. Hirose testified that he did not recall whether he had seen any other comparative data concerning the compounds tested in the Hirose declaration. [Tr. 1968-70 (Hirose)] Accordingly, Defendants have not proven that any individual knowingly withheld contradictory test data.

B. There Were No False Statements in the Hirose Declaration

Defendants' second argument in support of their unenforceability defense is that Dr. Hirose's declaration was allegedly false and misleading because Dr. Hirose did not follow the test procedures outlined in the protocol for the stereotypy testing attached as Exhibit 1 to his declaration. Again, Defendants have not proven that Dr. Hirose offered false statements with an intent to mislead.

1. The Hirose Protocol Accurately Described the Testing Procedures

In this protocol, Dr. Hirose indicated that the "observation for stereotyped behavior will be performed by an observer blind to the treatment received by the mice." [PTX 20 at OPC0001665] Defendants contend that this statement indicates that only a single observer conducted all of the stereotypy testing and that this single observer would be blinded to the identity of the compound being tested, not just the doses of the compounds administered. Because two observers conducted the stereotypy experiments and because these observers were blinded to the doses administered but not the compounds, Defendants argue that Dr. Hirose did not follow his study protocol and suggest he did so with an intent to deceive.

The protocol, however, does not support Defendants' interpretation. The isolated statement cited by Defendants merely indicates that individual mouse observations would be performed by a single individual. It does not state that only one individual would be involved in the overall conduct of the study, as Defendants contend. [PTX 20] To the contrary, the Hirose protocol specifically identifies two individuals, Dr. Hirose and Dr. Kikuchi, as the investigators who carried out the testing. Dr. Roth and Dr. Hirose each explained that it was therefore clear that two individuals would score the stereotypy testing. [Tr. 1100-01 (Roth); Tr. 1983-86 (Hirose); PTX 20 at OPC0001658]

Defendants did not offer any testimony in response to Dr. Roth's and Dr. Hirose's testimony in this regard. Dr. Beninger, Defendants' only witness on this issue, did not refer in any way to the listing of two investigators in the protocol and, in fact, did not provide any clear testimony in support of Defendants' position that the Hirose protocol indicated that only a single individual would perform the stereotypy testing. [Tr. 958 (Beninger)] Accordingly, Defendants have not shown that the protocol indicates that the testing would be performed by a single individual.

Defendants likewise did not establish that the protocol indicated that the observers would be blinded to the identity of the compound being studied. The statement in the protocol refers to the "treatment received by the mice." [PTX 20 at OPC0001665] Because the observers were blinded to the dosage of compound administered to the mice, or whether the mice were instead administered the placebo, they were in fact blinded to the treatment received by the mice. As Dr. Roth explained, the statement in the protocol does not necessarily indicate that the observer was blinded to both the identity of the compound and the dose of compound administered. [Tr. 1113-14 (Roth)] Moreover, as discussed above, Dr. Roth explained that the blinding methodology used by Dr. Hirose, where the

observer was blinded to the dose administered to the mice, was sufficient to effectively blind the study. [*Id.*]

Dr. Hirose similarly explained that the mention of blinding in the protocol was referring to the fact that the observer was in fact blinded to the dose of test compound administered to the mice, which was in fact the treatment received by the mice. [Tr. 1930-31 (Hirose)] As Dr. Hirose further explained, this blinding methodology was the standard method employed at Otsuka, and Otsuka had used this same blinding methodology in experiments conducted for generating data for submission to the FDA and for publications in peer-reviewed journal articles. [Tr. 1931-33 (Hirose)]

Therefore, Defendants have not proven that the Hirose protocol inaccurately described the experimental procedures. Moreover, as discussed above in Section IV.J.5.b.(2), Defendants have not shown the testing methodology used by Dr. Hirose rendered the data unreliable.

2. Dr. Hirose Did Not Intend to Deceive the PTO

Defendants also have not shown that Dr. Hirose acted with deceptive intent in conducting the testing underlying his declaration. Dr. Hirose testified that he followed the procedures outlined in the study protocol on many prior occasions, and that these were the typical methods employed by Otsuka. [Tr. 1931-1933 (Hirose)] Dr. Hirose explained that these were the same methods used in generating data for submission to the FDA and for publication in peer-reviewed journal articles. [Tr. 1931-1932 (Hirose)] Dr. Hirose had no reason to believe that these test procedures would not also be satisfactory for the PTO. Defendants have not established to the contrary, much less that Dr. Hirose acted with deceptive intent with respect to the conduct of the stereotypy testing.

Lacking any affirmative evidence, Defendants suggest that, because Dr. Hirose hoped that the data would be helpful for Otsuka, he must have intended to deceive the PTO. The evidence does not

support that conclusion. Every declarant hopes that their declaration and any included data will be supportive of patentability. That does not mean that every declarant acts with deceptive intent, and Defendants cannot establish through this argument that Dr. Hirose acted with an intent to deceive the PTO.

C. There Is No Evidence of Any Withholding of the Nakagawa Declaration

Defendants' third argument in support of their unenforceability defense is that the Nakagawa declaration was withheld from the PTO with deceptive intent. The Nakagawa declaration does not concern the type of testing discussed in the '528 patent and prosecution history, does not suggest the test results reported in the Hirose declaration, and further teaches away from the structural features of aripiprazole. There is also no evidence that this non-prior art document was withheld from the PTO, or that it was withheld with an intent to deceive.

1. The Nakagawa Declaration Does Not Bear on the Predictability of the Hirose Declaration Test Results

For purposes of their inequitable conduct arguments, Defendants contend that the mouse jumping test data in the Nakagawa declaration indicate the superiority of a butoxy linker group over a propoxy linker group in an improved antipsychotic drug, thus suggesting that the test results reported in the Hirose declaration were not unexpected. The Nakagawa test data do not support that conclusion. The Nakagawa declaration does not include testing of any of the compounds tested in the Hirose declaration. [DTX 214; PTX 20] Further, the mouse jumping data disclosed in the Nakagawa declaration are different from the stereotypy test data disclosed in the '528 patent and the Hirose declaration. [Tr. 1244-1246 (Roth)] Accordingly, the Nakagawa mouse jumping data cannot be directly compared with the data reported in the Hirose declaration.

Defendants also did not establish any relationship between the mouse jumping test data and the stereotypy test data and, in fact, there is no scientific correlation between results in one test with the other. [Tr. 1247-48 (Roth)] Defendants' expert Dr. Marshall offered speculative testimony that test results in these two tests may be correlated, but conceded on cross-examination that he never actually attempted any such correlation. [Tr. 2203 (Marshall)] Defendants further argued that test results in the mouse jumping test and the stereotypy test may be correlated because results in these tests each relate to anti-schizophrenic efficacy. The evidence introduced at trial established, however, that these two tests are not equivalent in this regard. Defendants contend that the unsubstituted butoxy compound displays excellent test results in the mouse jumping test. This same compound is virtually inactive in the stereotypy test, indicating that the allegedly "excellent" mouse jumping data do not predict excellent results in the stereotypy test. [Tr. 1229-1232, 1239-1240 (Roth); PTX 564 at 661 (compound no. 4)] Moreover, while the stereotypy test has been widely used in antipsychotic drug development, there is no evidence that the mouse jumping test has ever been used to develop a new antipsychotic drug. [Tr. 1243-44 (Roth); Tr. 253 (Press); Tr. 851-2 (Castagnoli)]

Even if there were a relationship between the mouse jumping data in the Nakagawa declaration and the stereotypy data presented in the Hirose declaration, the Nakagawa data do not show the general superiority of a butoxy linker group over a propoxy linker group as Defendants contend. Defendants focus on the mouse jumping data in the Nakagawa declaration relating to two compounds, the unsubstituted propoxy-linked compound and the unsubstituted butoxy compound. The mouse jumping test results concerning this pair of compounds do not establish the superiority of all butoxy-linked compounds, much less predict stereotypy test results for all butoxy-linked compounds. It was shown at trial that the butoxy-linked compound tested in the Nakagawa

declaration, the unsubstituted butoxy compound, has very low potency in the stereotypy test, negating any argument that the Nakagawa data would suggest the superiority of this compound in the stereotypy test. [Tr. 1229-1232, 1239-1240 (Roth); PTX 564 at 661 (compound no. 4)]

The Nakagawa test data were also insufficient to support the conclusions that Defendants seek to draw from those data for the reasons discussed above at Section IV.H.3.

Further, if anything, the data in the Nakagawa declaration teach away from the structural features of the claimed compounds tested in the Hirose declaration, including the use of a butoxy linker group. The most potent compound presented in the Nakagawa declaration, test compound 44, has the linker group attached at the 5-position on the carbostyril core, not the 7-position, like the claimed compounds tested in the Hirose declaration. [Tr. 1639-1640, 1642 (Nichols); DTX 214; PTX 20] Compound 44 is also a propoxy-linked compound, not a butoxy-linked compound. [Tr. 1642 (Nichols)] In fact, eight of the nine compounds tested in the Nakagawa declaration are propoxy-linked compounds. [Tr. 258 (Press); DTX 214] Therefore, if anything, the Nakagawa declaration teaches the superiority of, and a preference for, propoxy-linked compounds, not butoxy-linked compounds as alleged by Defendants.

The irrelevance of the Nakagawa mouse data is further established by the course of the reexamination proceedings relating to the '528 patent. During the reexamination proceedings, Otsuka submitted the Banno article, which included mouse jumping data for a number of compounds, including two of Defendants' proposed lead compounds (the unsubstituted butoxy compound and OPC-4392), and also the compounds included in the Nakagawa declaration. [Tr 537-552 (Goolkasian); DTX 214 at 4384 and 4386; DTX 84] The Examiner did not cite to any of these mouse jumping data in the reexamination proceedings, confirming that these data, which were distinct from

the stereotypy data disclosed in the '528 patent and presented in the Hirose declaration, were not relevant to the patentability of the '528 patent claims. [DTX 121]

Defendants cite to the testimony of their patent expert, Mr. Goolkasian, in support of their argument for the materiality of the Nakagawa declaration. Mr. Goolkasian, however, lacked the technical expertise to offer any opinion concerning the import of the mouse jumping data presented in the Nakagawa declaration. [Tr. 546 (counsel for Defendants objecting and asserting about Mr. Goolkasian: "this is a patent law expert . . not a medicinal chemist . . .the witness is incompetent to answer the question [concerning a comparison of mouse jumping data]")]

Mr. Goolkasian also failed to appreciate that the Nakagawa declaration and the Banno article contained mouse jumping data for the same compounds. [DTX 214; DTX 84] On cross-examination, Mr. Goolkasian was asked if he was aware of the relationship between the data in the Nakagawa declaration, about which he testified on direct examination, and the data in the Banno article. His response was, "Which is the Banno paper?" [Tr. 530-31 (Goolkasian)] He then confirmed, "No, I am not." [Tr. 531 (Goolkasian)] He was asked if he had read the Banno paper and replied, "I scanned through it, I believe." [Tr. 531 (Goolkasian)] He did not mention the Banno article in his expert reports. [Tr. 531 (Goolkasian)] Later in his testimony he said, "I really haven't studied the reference, and it takes me a long time to study." [Tr. 537 (Goolkasian)]

Considering the foregoing, the Court does not credit Mr. Goolkasian's testimony concerning the materiality of the Nakagawa declaration.

2. There Is No Evidence of Any Withholding of the Nakagawa Declaration

The evidence also does not establish, as Defendants contend, that any individual withheld the Nakagawa declaration from the PTO with an intent to deceive. Defendants have only identified a

single individual in their allegations of the alleged withholding of the Nakagawa declaration: Dr. Oshiro. Dr. Oshiro denied any knowledge of the Nakagawa declaration [Tr.1861-62] and Defendants have not pointed to any credible evidence to the contrary.

The deposition testimony of Dr. Nakagawa that Defendants cite does not establish that Dr. Oshiro knew of the Nakagawa declaration. Dr. Nakagawa denied that Dr. Oshiro would have had a central role in preparing this declaration and stated only that he "might have been involved as a co-worker." [Nakagawa Dep. Tr. 140:21-25] This speculative testimony is insufficient to cast any doubt on Dr. Oshiro's clear denial of any knowledge of this declaration.

Defendants also point to Dr. Oshiro's testimony that he was aware of mouse jumping data for the unsubstituted butoxy compound. This testimony does not establish, however, that Dr. Oshiro was aware of the Nakagawa declaration, the specific document Defendants have alleged was withheld. Dr. Oshiro stated that the mouse jumping data he was aware of for the unsubstituted butoxy compound was not the same as that reported in the Nakagawa declaration. [Tr. 1868 (Oshiro)] The record reflects that Dr. Oshiro authored the Banno article, which contained mouse jumping data concerning the unsubstituted butoxy compound, among other compounds, though the mouse jumping data for the unsubstituted butoxy compound reported in the Banno article (9.5 mg/kg) was different from that reported in the Nakagawa declaration (5.5 mg/kg) . [Tr. 531-543 (Goolkasian); DTX 84] This explains how Dr. Oshiro could know of data for the unsubstituted butoxy compound, but not know of the Nakagawa declaration. [DTX 84]

The Banno article also does not support Defendants' arguments that mouse jumping data predict the superiority of butoxy-linked compounds. The Banno article reported that the propoxy-linked compounds had potencies that were greater than or equal to the butoxy-linked compounds.

[DTX 84 at 4385; Tr. 545-47 (Goolkasian)] Thus, the Banno article and the mouse jumping data that Dr. Oshiro was aware of did not suggest the superiority of butoxy-linked compounds over propoxy-linked compounds. The Banno article was submitted to the PTO during the reexamination proceedings [DTX 121] and Defendants have not alleged any withholding of this document.

D. There Were No False Statements During the Reexamination Proceedings

Defendants' final argument in support of their unenforceability defense is that Otsuka's representatives made allegedly false statements to the PTO during the reexamination proceedings. Again, the evidence presented at trial does not support a conclusion that any individual knowingly presented false statements during the reexamination proceedings.

1. The Identified Statements Were Not False

Defendants point to arguments Otsuka's representatives presented in a May 16, 2005 Amendment and a September 14, 2005 Request for Reconsideration. In these submissions, Otsuka's representatives responded to various claim rejections, including a claim rejection based on five exemplary compounds disclosed in the '416, '840 and DE '105 patents. [DTX 121] Defendants quote Otsuka's representative's argument, presented in each of these submissions, that "there is no evidence that the five exemplary carbostyril derivatives identified by the Examiner have . . . the recited property of treating schizophrenia." Defendants contend that this argument is allegedly contradicted by mouse jumping data in the Nakagawa declaration, a document that was not before the PTO during the reexamination proceedings. [Def. FOFCOL, page 70; DTX 214]

Defendants' argument relies on a cropped quotation from these documents. The full argument concerning these five compounds disclosed in the '416, '840 and DE '105 patents, as set forth in the May 16, 2005 Amendment, actually reads as follows:

> Fourth, while these references may suggest that their compounds may be useful for treating central nervous disorders, generally, there is no evidence that the five exemplary carbostyril compounds identified by the Examiner have such properties, let alone the recited property of treating schizophrenia. In fact, all of the testing is directed to very different properties, such as antihistamine, anaesthesia, and analgetic activities. *See* Exhibit C ['416 patent] at Col 31, line 1 to col. 36, line 10.

[DTX 121 at 01274] This same argument is repeated in abbreviated fashion in the Request for Reconsideration, along with a citation to the full argument presented in the May 16, 2005 submission. [DTX 121 at 01348]

This full uncropped statement makes clear that Otsuka's representatives were referring to the documents that were the subject of the PTO's claim rejection, the '416, '840 and DE '105 patent, and the lack of experimental evidence in these documents concerning the treatment of schizophrenia. This statement is factually correct and Defendants have introduced no evidence to the contrary. There was no dispute among the parties that the cited references did not contain any experimental evidence that any of the disclosed compounds had the property of treating schizophrenia. [Tr. 1208 (Roth); Tr. at 129 (Press) ("there is no data in the '416 patent with respect to antipsychotic activity")] Thus, even accepting Defendants' interpretation of the Nakagawa test data, the full statement from the reexamination submissions is not in conflict with the Nakagawa declaration as Defendants suggest.

2. There Is No Evidence That the Identified Statements Were Intended to Mislead

Defendants also have not offered any evidence that any individual was aware of the contradiction they allege in the identified statements or intended to mislead the PTO in offering these statements. Defendants focus on Dr. Oshiro, but there is no evidence that Dr. Oshiro reviewed these reexamination documents prior to their submission, was aware of these specific statements, or acted

with any deceptive intent. Dr. Oshiro testified at trial that he did not remember providing any comments concerning the May 16, 2005 Amendment, and Defendants never inquired as to the September 14, 2005 Request for Reconsideration. [Tr. 1892 (Oshiro)]

Lacking any evidence concerning these documents, Defendants argue that Dr. Oshiro was "intimately involved with the reexamination proceeding." The record does not support that conclusion. The evidence establishes that Dr. Oshiro did attend certain meetings concerning the reexamination proceedings and also exchanged certain written communications. As Dr. Oshiro explained, however, given his hearing disability, his attendance at meetings did not mean he was fully aware of the discussions that took place during those meetings. [Tr. 1874-1875 (Oshiro)] Moreover, Defendants did not establish that Dr. Oshiro participated in the preparation of any specific documents submitted during the reexamination. [Tr. 1875 (Oshiro)] Defendants have not proven that Dr. Oshiro acted with deceptive intent.

VI. CONCLUSIONS OF LAW

A. Obviousness

1. Legal Standard for Obviousness Under 35 U.S.C. § 103(a)

An issued patent is presumed valid. 35 U.S.C. § 282. The burden of proof to support an allegation of invalidity, including an allegation of obviousness under 35 U.S.C. § 103(a), rests upon the accused infringers (the Defendants in this case). *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1355 (Fed. Cir. 2007). This burden must be met by clear and convincing evidence. *Id*.

Obviousness under 35 U.S.C. § 103(a) is ultimately a legal question, but is based on underlying factual determinations. *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356

(Fed. Cir. 2008). The factual determinations underpinning the legal conclusion of obviousness include (1) "the scope and content of the prior art," (2) "the level of ordinary skill in the art," (3) "the differences between the claimed invention and the prior art," and (4) "evidence of secondary factors, also known as objective indicia of non-obviousness." *Eisai*, 533 F.3d at 1356 (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). "While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls." *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 407 (2007).

The U.S. Supreme Court recently clarified certain principles concerning obviousness determinations under 35 U.S.C. § 103 in its decision in *KSR,* 550 U.S. 398. Following the *KSR* decision, the Federal Circuit has applied these principles in several cases addressing obviousness challenges to patent claims covering chemical compounds. As the Federal Circuit recently explained, when a patent claims a chemical compound, a *prima facie* case of obviousness under the third *Graham* factor frequently turns on the structural similarities and differences between the compounds claimed and those in the prior art. *Daiichi*, 2010 U.S. App. LEXIS 18820 at *11. A *prima facie* case of obviousness for a chemical compound begins with the reasoned identification of a lead compound. *Eisai*, 533 F.3d at 1359. "While the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound, the analysis still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art." *Daiichi*, 2010 U.S. App. LEXIS 18820 at *18 (internal citation omitted).

"[I]t is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds. Yet the attribution of a compound as a lead

compound after the fact must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention." *Id*. at *16-17 (citing *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)). Thus, a compound may not be properly identified as a lead compound merely because it is structurally similar to the claimed compound. "[P]roving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds." *Id*. at *17 (citing *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1377-79 (Fed. Cir. 2006)). "Potent and promising activity in the prior art trumps mere structural relationships." *Id*. In addition "negative side effects could dissuade one of skill from using a particular compound as a starting point." *Eisai*, 533 F3d at 1358.

Once the lead compound or compounds have been identified, it is "necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Takeda*, 492 F.3d at 1357. Thus, proof of obviousness requires clear and convincing evidence that one of ordinary skill in the art would have been motivated to both select the particular lead compound or compounds and also motivated to modify the lead compound or compounds to achieve the claimed compound "with a reasonable expectation that the new compound would have similar or improved properties compared with the old." *Daiichi*, 2010 U.S. App. LEXIS 18820 at *11-12. To the extent an art is unpredictable, as the chemical arts often are, potential solutions are less likely to be genuinely predictable. *Eisai*, 533 F3d at 1359. In determining what would have been obvious to one of ordinary skill in the art at the time of the invention, the use of hindsight is not permitted. *KSR*, 550 U.S. at 421 (cautioning against "the

distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness).

In keeping with the flexible nature of the inquiry after *KSR*, the motivation to select and modify a lead compound need not be explicit in the art. *Daiichi*, 2010 U.S. App. LEXIS 18820 at *12 (citing *Eisai*, 533 F.3d at 1357 and *Takeda*, 492 F.3d at 1356-57). However, a court's analysis of the motivation to modify the prior art should be made explicit (*KSR*, 550 U.S. at 418), and a flexible application of the teaching, suggestion, motivation test remains "the primary guarantor" against non-statutory hindsight analysis. (*Ortho-McNeil*, 520 F.3d at 1364).

Evidence of secondary factors, also known as objective indicia of non-obviousness, must also be considered. Such evidence "is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness." *Ortho-McNeil*, 520 F.3d at 1365. Such objective evidence can include evidence of long-felt but unmet need, failures of others, commercial success, copying, unexpected results, and industry acclaim. *Graham*, 383 U.S. at 17-18. In some cases, such objective evidence may be the most probative and cogent evidence of nonobviousness in the record. *Ortho-McNeil*, 520 F.3d at 1365 (citing *Catalina Lighting, Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002) (internal citation omitted)).

2. Person of Ordinary Skill in the Art

This Court recently determined the level of ordinary skill in the art with respect to a patent directed to antipsychotic pharmaceutical compounds. *Janssen*, 456 F. Supp. 2d at 654. This Court concluded, as Otsuka urges here, that the level of ordinary skill in the art is "a master's degree in chemistry, medicinal chemistry, or pharmacy, or a bachelor's degree in one of those fields with at least two years of experience in researching antipsychotic drugs." *Id.* In reaching this conclusion,

the Court rejected defendant's exceptionally high proposed level of ordinary skill: that of a "Ph.D. with at least two years of experience and a record of research success, which is attested to by a small group of publications." *Janssen*, 456 F. Supp. 2d at 653. The Court was persuaded by testimony that "actual workers involved in the development of antipsychotic compounds have bachelor's or master's degrees, not doctorate degrees," and opted for Janssen's lower proposed level of ordinary skill. *Janssen*, 456 F. Supp. 2d at 654.

Although this Court decided the level of ordinary skill in *Janssen* with respect to a patent having a 1985 priority date, while the '528 patent's priority date is in 1988, Defendants have submitted no evidence suggesting that the level of ordinary skill escalated at all within that extremely short time frame. Moreover, Dr. Roth's testimony is consistent with the testimony in *Janssen* that the Court found persuasive, in that Dr. Roth testified that actual workers in this area have bachelor's and master's degrees. [Tr. 1120-23 (Roth)]

The Court is unpersuaded by Defendants' argument for a higher standard for a person of ordinary skill in the art. Defendants' argument that the hypothetical person having ordinary skill is a team composed of multiple individuals cannot be reconciled with the language of 35 U.S.C. § 103(a). "[A] patent may not be obtained … [if] the subject matter as a whole would have been obvious at the time the invention was made to *a person having ordinary skill in the art* to which said subject matter pertains." 35 U.S.C. § 103(a) (emphasis added). The U.S. Supreme Court also uses a single hypothetical person of ordinary skill in its obviousness analyses, not a plural construct. "If *a person* of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability." *KSR*, 550 U.S. at 401 (emphasis added); *see also Graham*, 383 U.S. at 14.

Endowing this hypothetical person with the collective knowledge and experience of an innovative research team tasked with developing new inventions is also irreconcilable with the plain meaning of "ordinary skill." "While the person having ordinary skill knows all of the prior art, s/he is neither a genius nor an innovator." *Janssen*, 456 F. Supp. 2d at 653; *Pfizer Inc. v. Teva Pharms. U.S.A., Inc.*, 482 F. Supp. 2d 390, 422 (D.N.J. 2007); *see also Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000).

> A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which.

Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985). The U.S. Supreme Court has clarified that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton," but has not departed from the notion that a person of ordinary skill in the art is in fact ordinary. *KSR*, 550 U.S. at 421.

Accordingly, for the foregoing reasons, the Court concludes that a person of ordinary skill in the art of antipsychotic drug discovery in October 1988 would be an individual having a master's degree in chemistry, medicinal chemistry, or pharmacy, or a bachelor's degree in one of those fields with at least two years of experience in researching antipsychotic drugs. The person of ordinary skill would not comprise a "team" of Ph.D. scientists as Defendants propose.

3. Scope and Content of the Prior Art

As discussed above in Sections IV.B and IV.C, the Court concludes that one of ordinary skill in the art, interested in developing a new antipsychotic drug in October, 1988, would have chosen as a lead compound for development a compound based on an existing antipsychotic drug such as

clozapine or risperidone. The Court further concludes that one of ordinary skill in the art would not have focused on an unproven class of compounds such as carbostyrils. Accordingly, the Court concludes that the prior art asserted by Defendants, which all concerns carbostyrils, aside from the Parke-Davis coumarin work, is not the most relevant prior art for the Court's obviousness inquiry and reflects an improper hindsight-based approach. The Court further concludes that two documents upon which Defendants rely are not prior art.

a. Defendants Failed to Establish With Clear and Convincing Evidence that the Nakagawa Declaration Is Prior Art

Defendants contend that the Nakagawa declaration, a document submitted during the prosecution of the '416 patent is a "printed publication" that was prior art within the meaning of 35 U.S.C. § 102(b) as of the date of issuance of the '416 patent, March 29, 1988. Defendants bear the burden of proving by clear and convincing evidence that the Nakagawa declaration constitutes prior art. For the following reasons, Defendants have not met that burden.

(1) Legal Standard for a Printed Publication Under 35 U.S.C. § 102(b)

For a document to qualify as a "printed publication" within the meaning of § 102(b) and thus constitute prior art, it "must have been sufficiently accessible to the public interested in the art; dissemination and public accessibility are the keys to the legal determination whether a prior art reference was 'published.'" *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989) (citations omitted). "A reference is considered publicly accessible if it was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (citation and quotation marks omitted); *see also SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1197 (Fed.

Cir. 2008).

A document is not a printed publication if it was not generally available to the public prior to the critical date. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 936-37 (Fed. Cir. 1990) (holding that documents housed in library accessible only to certain authorized persons were not generally available by the exercise of reasonable diligence and therefore not printed publications). A document also is not a printed publication if, while it is generally available to the public, it is not cataloged or indexed in any meaningful way or otherwise capable of being located by an individual interested in the subject matter exercising reasonable diligence. *See Cronyn*, 890 F.2d at 1161 (holding that theses located in a university library were "not accessible to the public because they had not been either cataloged or indexed in a meaningful way."); *Lister*, 583 F.3d at 1312-14 (vacating and remanding question of whether document was printed publication where it was undisputed that the document was available for public inspection but unclear whether it was included in a public database such that it could be located by persons interested and ordinarily skilled in the art exercising reasonable diligence).

(2) Defendants Have Not Proven That the Nakagawa Declaration Was Publicly Accessible as of the Critical Date

Defendants have not presented any evidence that the Nakagawa declaration was publicly available by the October 31, 1988 priority date. The '416 patent indicates that it issued on March 29, 1988, approximately seven months before the critical date. After issuance, a member of the public could have asked the PTO to review the PTO's internal file regarding the prosecution of the '416 patent if and when it became available following internal PTO processing associated with issuance of the '416 patent. *See* C.F.R. § 1.11 (indicating that prosecution files of issued patents are open to

the public, but not specifying when the files become available upon patent issuance). Defendants presented no evidence, however, that anyone ever made such a request or that the single copy of the '416 prosecution history located in the PTO's files was ever copied or disseminated to any member of the public during that seven-month period prior to the critical date. Defendants also presented no evidence that the prosecution history was in fact available for inspection during that time period. In fact, despite acknowledging that the public availability of the '416 patent prosecution history as of the issuance of the '416 patent was a disputed matter of fact [July 23, 2010 Hr'g Tr. 42:15-43:2], Defendants made no effort at trial to prove this fact. [Tr. 25-26] Defendants presented no documents relevant to this issue and Defendants' expert in Patent Office practice and procedure, Mr. Goolkasian, did not mention this issue in his testimony. Defendants have therefore failed to prove public availability of the '416 patent file history, including the Nakagawa declaration.

(3) Defendants Have Not Proven That a Person of Ordinary Skill in the Art Interested in the Subject Matter Could Have Located the Nakagawa Declaration

Even if the '416 file history and its contents were deemed publicly available prior to October 31, 1988, Defendants have not established by clear and convincing evidence that persons interested and of ordinary skill in the subject matter or art exercising reasonable diligence could have located the Nakagawa declaration. Defendants have not identified any database or indexing of the contents of the '416 patent prosecution history that would have led one of one of ordinary skill to this patent prosecution history and allowed them to locate the Nakagawa declaration among the 1561 pages of this patent prosecution history. [DTX 333] Moreover, Defendants' experts did not provide any testimony explaining how one of ordinary skill in the art would have been able to locate this document. In fact, Dr. Press and Dr. Castagnoli each testified that they had not independently located

the Nakagawa declaration, and Dr. Castagnoli acknowledged that he had conceded during his deposition that he did not know how to locate a document contained in a file history. [Tr. 846-48 (Castagnoli); Tr. 248-50 (Press)]

Notwithstanding this absence of any testimony on this point, Defendants contend that the reference to "antischizophrenia agents" in the '416 patent "is sufficient to guide the skilled person to the Nakagawa Declaration in the prosecution history of the '416 patent." [Def. FOFCOL, page 84] But the '416 patent contains only a single reference to "antischizophrenia agents" throughout its forty-four pages, on the fourth page among a list of nine other potential central nervous system controlling uses for the claimed compounds. [DTX 6 at col. 3, ll. 13-22.] Moreover, while the '416 patent specification does include test data relevant to some of the disclosed uses of the compounds, it is undisputed that the specification does not include any test data relevant to antipsychotic activity. [Tr. 129 (Press) ("there is no data in the '416 patent with respect to antipsychotic activity")] Nothing in the '416 patent specification indicates that any testing for "antischizophrenia agents" was ever conducted, or that any such tests were submitted to the PTO. [*Id*. at cols. 1-84] Defendants did not present any evidence in support of their theory that one of ordinary skill in the art would have been motivated to look for the Nakagawa declaration based on this isolated reference to "antischizophrenia agents" or that one of ordinary skill in the art would have successfully located this document. Defendants have failed to show that one of ordinary skill in the art could have located the Nakagawa declaration based on the limited information in the '416 patent.

(4) The Cases Defendants Cite Are Distinguishable

Lacking supporting facts, Defendants rely primarily on three cases in support of their position: *Takeda*, 492 F.3d 1350, *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374 (Fed. Cir. 2004) and

Bamberger v. Cheruvu, 55 U.S.P.Q.2d 1523 (B.P.A.I. 1998). The facts in these cases are distinguishable from those in the present case, and therefore this case law does not support Defendants' position that the Nakagawa declaration constitutes prior art and cannot make up for Defendants' lack of proof on this issue.

The Defendants first cite to *Takeda*, a case in which the Federal Circuit stated in dicta that a preliminary amendment in a patent file history constituted relevant prior art. *Takeda* is not a case concerning printed publications under § 102(b) in that the *Takeda* Court did not specifically address this issue in its decision and it is unclear whether this point was even disputed by the parties. *See Takeda*, 492 F.3d at 1363. In particular, there is no mention in *Takeda* of any dispute between the parties as to whether the file history was publicly accessible during an abbreviated period, such as the seven-month period here between the '416 patent issuance and the '528 patent priority date. *Id*. There is also no mention in *Takeda* of any dispute as to whether one of ordinary skill in the art would have been led to the file history and the specific document at issue in that case. In addition, the Court did not rely on the prior art status of the prosecution history at issue in rendering its decision, because it determined that the patent claims were non-obvious even if this prosecution history were part of the prior art. The Court's statement in *Takeda* is therefore dictum, and given these significant differences between the facts of the present case and those in *Takeda* this decision does not suggest that this Court should hold in this case that the Nakagawa declaration is prior art.

In *Bruckelmyer*, the next case cited by Defendants, a divided panel of the Federal Circuit held that two drawings included as part of a patent application filed in the Canadian Patent Office, but removed from the issued patent, constituted printed publications. 445 F.3d at 1376. The present facts, however, do not concern the contents of a patent application. The Nakagawa declaration was

not part of the '416 patent application as filed in the PTO. The *Bruckelmyer* Court also expressly cautioned against applying its decision beyond the facts of the case, stating that it had no opinion on other situations, including where the document at issue "is contained in a foreign file wrapper, but otherwise bears little relation to the subject matter of the issued and published patent." 445 F.3d at 1379 n.3. Consistent with this caution, in later decisions the Federal Circuit has narrowly construed *Bruckelmyer*. *See, e.g.*, *SRI*, 511 F.3d at 1196 (stating "in Bruckelmyer, this court found that a Canadian patent application, properly abstracted, indexed and catalogued, was a printed publication under §102(b).") The PTO similarly considers the *Bruckelmyer* decision limited to the specific question addressed, i.e., whether portions of a patent application as originally filed constitute prior art. *See* MPEP 2127(II) ("Figures that had been cancelled from a Canadian patent application before issuance of the patent were available as prior art under 35 U.S.C. 102(b) as of the date the application became publicly accessible." (citing *Bruckelmyer*, 445 F.3d 1374) (emphasis added).

Further, in *Bruckelmyer*, the Federal Circuit found that a specific reference to a particular use for a disclosed heating system in the issued patent would have led a person skilled in the art to the underlying patent application and the two drawings contained therein, because the two drawings illustrated that specifically described use. 445 F.3d at 1376. Here, in contrast, the '416 patent would not have led a person of ordinary skill to search for or locate the Nakagawa declaration within the patent prosecution history. Accordingly, *Bruckelmyer* does not support any conclusion that the Nakagawa declaration constitutes prior art.

Bamberger, the final case cited by Defendants, is even less relevant to the Court's analysis of the prior art status of the Nakagawa declaration. *Bamberger* is a decision of the Board of Patent Appeals and Interferences concerning an interference proceeding at the PTO, not a district court

proceeding concerning patent validity. The burden of proof in determining the obviousness issue in this interference was preponderance of the evidence, not clear and convincing evidence as in the present case. In *Bamberger*, in considering the obviousness question according to that lower standard of proof, the PTO assumed that a declaration submitted in a file history was prior art. 55 U.S.P.Q.2d at 1537 n.22. There is no indication, however, that the parties disputed the prior art status of this document. For example, the PTO raised concerns regarding the admissibility of the declaration during an evidentiary hearing, but neither of the parties objected to its admissibility, and it was therefore allowed in evidence. *Id*. at 1533 n.14. The prior art status of this document also did not factor into the PTO's final decision because the PTO ultimately refused to find the disputed patent claims obvious over this declaration. The PTO's statement concerning the prior art status of this document was therefore dictum. *Id*. at 1537. Again, given the significant difference between the facts of the present case and those in *Bamberger*, the decision in the *Bamberger* case does not suggest that the Nakagawa declaration constitutes prior art.

Accordingly, the cases Defendants cite do not establish that the Nakagawa declaration constitutes prior art.[5] Nor do they support any general proposition that documents in prosecution histories are printed publications under 35 U.S.C. § 102. The prior art status of particular documents must be analyzed under the specific relevant facts. *Cronyn*, 890 F.2d at 1161 (holding that "[t]he decision whether a particular reference is a printed publication must be approached on a case-by-case

[5] Alternatively, Defendants summarily contend that the Nakagawa declaration is prior art under 35 U.S.C. § 102(a). [*See* Def. FOFCOL, page 84, n.13] Defendants, however, do not provide any evidence that the Nakagawa declaration was "known or used by others" in the United States by the critical date. Defendants do not even identify the persons in the United States who allegedly knew or used the information in the Nakagawa declaration by the critical date. Defendants' § 102(a) assertion is therefore unavailing.

basis") (citations omitted). Under the relevant facts here, Defendants have failed to carry their burden of proving that the Nakagawa declaration was publicly available and accessible by one of ordinary skill in the art interested in the subject matter exercising reasonable diligence.

b. Defendants Failed to Establish With Clear and Convincing Evidence That the Wise Poster Is Prior Art

As with the Nakagawa declaration, Defendants bear the burden of proving by clear and convincing evidence that DTX 398, "the Wise poster," is a "printed publication" under 35 U.S.C. § 102(b) and therefore constitutes prior art. *Carella v. Starlight Archery & Pro Line Co.*, 804 F.2d 135, 138-39 (Fed. Cir. 1986). For poster presentations, the Federal Circuit has held that the public accessibility of the poster and therefore its status as a prior art printed publication under § 102(b), is analyzed according to a multi-factor test in which the court considers: whether copies of the presentation were distributed and also "the length of time the display was exhibited, the expertise of the target audience, the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied, and the simplicity or ease with which the material displayed could have been copied." *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed Cir. 2004).

In support of their argument that the Wise poster is a printed publication, Defendants contend that the Wise poster was publicly displayed and distributed at the November 1987 annual meeting of the Society of Neurosciences in New Orleans, Louisiana. Defendants failed to introduce at trial any viable evidence in support of this argument and therefore failed to establish that the Wise poster constitutes prior art.

(1) Dr. Wise's Deposition Testimony Is Inadmissible Hearsay

The only direct evidence Defendants cite in support of their argument for the prior art status of the Wise poster is the deposition testimony of Dr. Lawrence Wise. Dr. Wise's deposition testimony, however, is inadmissible hearsay and Defendants have not shown that his testimony falls into any of the exceptions to the hearsay rule. Among other things, Defendants have not made any showing that Dr. Wise was unavailable to appear to testify live at trial. To the contrary, Defendants indicated in the Pretrial Order that Dr. Wise, who is a paid consultant for Defendants (Wise Dep. Tr. 61:22-62:4; 62:9-17; 63:4-10; 64:7-21; 65:7-13), would testify live at trial. [Final Pretrial Order (D.I. 328) at pages 136-37] Dr. Wise's unexplained absence at trial, coupled with Dr. Wise's failure to respond to relevant questions at his deposition as explained in more detail below, clearly curtailed Otsuka's right to cross-examine Dr. Wise. Dr. Wise's deposition testimony is thus accorded little weight, if any. *See Derewecki v. Pa. R.R. Co.*, 353 F.2d 436, 442 (3d Cir. 1965) (noting "that the right of cross-examination inheres in every adversary proceeding and that it is established beyond any necessity for citation of authorities . . . that if cross-examination of an available witness is not had the litigant, deprived of cross-examination, has been denied due process of law"); *United States v. Alvarez*, No. 09-0319, 2010 U.S. Dist. LEXIS 2456, at *10 (D.N.J. Jan. 13, 2010) (noting that "[t]he right to meaningful cross-examination can hardly be overemphasized" and that "[s]tatements of a testimonial nature, such as depositions, are not admissible at trial unless the witness is unavailable and the [party] has had a meaningful opportunity to cross-examine the witness about the statements"). Accordingly, Dr. Wise's deposition testimony cannot carry Defendants' burden of establishing that the Wise poster constitutes prior art.

(2) Dr. Wise's Testimony Cannot Satisfy Defendants' Burden Because That Testimony Was Not Corroborated, Was Impeded By Defendants, and Was Insufficient to Establish Dissemination

Even if Defendants had established that Dr. Wise's deposition testimony fell within an exception to the hearsay rule, this testimony cannot satisfy Defendants' burden because it is uncorroborated, because Defendants obstructed Otsuka's examination of Dr. Wise during his deposition, and because the testimony Dr. Wise did provide was insufficient to carry Defendants' burden.

Defendants failed to provide any evidence corroborating Dr. Wise's testimony that he publicly disseminated his poster in 1987. "The law has long looked with disfavor upon invalidating patents on the basis of mere testimonial evidence absent other evidence that corroborates that testimony." *Finnigan Corp. v. ITC*, 180 F.3d 1354, 1366 (Fed. Cir. 1999). Accordingly, "corroboration is required of any witness whose testimony alone is asserted to invalidate a patent, regardless of his or her level of interest." *Id*. at 1369. The Federal Circuit has specifically required corroboration of testimony, such as that offered by Dr. Wise, purporting to establish the date of printed publications. In *TypeRight*, the Federal Circuit reversed summary judgment for obviousness because the asserted prior art, an undated document alleged to have been distributed at a trade show eighteen years earlier, was discovered in a testifying witness's later-dated files and the corroborating witnesses offered only faulty and tentative testimony regarding the date of the document. *TypeRight Keyboard Corp. V. Microsoft Corp*., 374 F.3d 1151, 1158 (Fed. Cir. 2004). The court noted that both corroborating witnesses were paid by a party-in-suit, and concluded that even if the jury found these witnesses

credible, "the district court will still have to address whether the legal requirement of corroboration has been met." *Id.* at 1158-59.

Just as in *TypeRight*, the document in question here, the Wise poster, is undated. The document does bear a citation to the published abstract (#1289 Soc. Neurosciences Abst. 13: 359 1987) but this citation to this separate document does not date the Wise poster other than establishing that this document was generated after the citation information for the abstract became available. Critically, it is impossible to determine from the document whether it was generated or disseminated prior to the critical date. Moreover, even if some version of this document was generated prior to the critical date, it is impossible to determine whether that is the same version that was ultimately provided to Defendants, DTX 398. Defendants did not provide any supporting evidence to corroborate Dr. Wise's testimony on these key points. In fact, unlike the deficient evidence offered in *TypeRight*, where two witnesses provided tentative corroborating testimony, Defendants offered no corroborating testimony. *See TypeRight*, 374 F.3d at 1159-60.

Defendants argue there is no corroboration requirement, citing *In re Klopfenstein*, 380 F.3d 1345 (Fed. Cir. 2004) and *MIT v. AB Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). [*See* Def. FOFCOL, pages 86-88] These cases, however, are easily distinguishable in that the factual issues were not in dispute in those cases and therefore the requirement for corroboration was not implicated. In *Klopfenstein*, the Federal Circuit made clear "there are not factual disputes between the parties in this appeal [and] the legal issue of whether the Liu reference is a 'printed publication' will be reviewed de novo." 380 F.3d at 1348. Similarly, in *MIT*, the issue revolved around whether, given the facts found by the ITC, "the Birmingham paper is not prior art because it is not a 'printed publication' within the meaning of 35 U.S.C. § 102(b)." 774 F.2d at 1109. The ITC found, and the Federal

Circuit agreed, that the Birmingham paper was a printed publication based on the facts which apparently were undisputed. *MIT*, 774 F.2d at 1108-09. In stark contrast, the present case raises a factual dispute, *i.e.*, whether Dr. Wise in fact publicly presented and distributed at the 1987 conference in Louisiana the Wise poster (DTX 398) presented at trial. Accordingly, under *Finnigan* and *TypeRight*, corroboration is required.

Defendants suggest that the Haruki memo corroborates Dr. Wise's testimony because it contains information consistent with the Wise poster and Dr. Wise's testimony. [*See* Def. FOFCOL, page 88] Mere consistency, however, does not constitute corroboration, and Defendants have not cited any case law to support their position. Indeed, Defendants have not established that the Wise poster could have been the only source of information included in the Haruki memo. The Haruki memo therefore does not establish that Dr. Wise publicly made available the Wise poster during the 1987 meeting in New Orleans. Importantly, the Haruki memo does not include most of the information found in the Wise poster, including all the actual experimental data points which play an integral role in Defendants' invalidity theories. Given the totality of the circumstances, the Haruki memo fails to corroborate Dr. Wise's testimony regarding the alleged public dissemination, prior art status and authenticity of the Wise poster.

Further compounding the unreliability of Dr. Wise's uncorroborated deposition testimony, counsel for Defendants significantly impeded counsel for Otsuka's ability to cross-examine Dr. Wise during his deposition. Defendants' counsel instructed Dr. Wise not to answer questions regarding the authenticity and alleged prior art status of the Wise poster (DTX 398), in contravention of the Court's order that Dr. Wise be deposed on that very topic. (Eighth Pretrial Scheduling Order, D.I. 300 at ¶ 7.) For example, when Otsuka asked Dr. Wise where the copy of the Wise poster that Dr. Wise

provided in connection with this litigation originated, counsel for Defendants improperly instructed Dr. Wise not to answer the question. (Wise Dep. Tr. 40:4-42:22.) Likewise, when Otsuka asked Dr. Wise when the copy of the Wise poster that Dr. Wise provided in connection with this litigation was created, counsel for Defendants improperly instructed Dr. Wise not to answer the question. (Wise Dep. Tr. 44:7-45:3.)

These questions were important to establishing whether or not the undated document Defendants used at trial, DTX 398, is in fact the same document that Dr. Wise contends was distributed in 1987. If Dr. Wise had conceded in response to this questioning that the document he had provided to Defendants for use in this litigation had been generated (e.g., printed) sometime well after 1987, this would have suggested the possibility that this document had been altered at some point in time, perhaps for purposes of a later presentation. Moreover, counsel for Defendants' obstruction of this line of inquiry strongly suggests that the answers to these questions would have established these problems with the document's authenticity.

To the extent that Defendants permitted Dr. Wise to respond to the questions at deposition, Dr. Wise's responses establish Dr. Wise's unclear recollection of the circumstances surrounding the New Orleans conference at which the Wise poster was purportedly disseminated.[6] For this reason as well, Dr. Wise's deposition testimony does not provide clear and convincing evidence of the prior art status of the Wise poster. Specifically, Dr. Wise testified at his deposition that he could not remember how many people actually visited his booth during the 1987 New Orleans conference, and Dr. Wise could

[6] Defendants disagree and point to deposition testimony of Dr. Wise that supports their contention that Dr. Wise disseminated the Wise poster at the New Orleans conference. Dr. Wise, however, did not appear at trial and the Court accordingly was not in a position to assess his credibility. For this reason and the fact that Otsuka's right to cross-examine Dr. Wise was severely hampered, Dr. Wise's testimony is not credited.

not recall the names of anyone who might have visited his booth during this conference. (Wise Dep. Tr. 21:18-22:2.) Dr. Wise speculated that he distributed "[i]n excess of a hundred" copies of his poster during the New Orleans conference but could not recall how many copies he actually brought or distributed and could not recall the names of any conference attendees who may have obtained copies of his poster. (Wise Dep. Tr. 30:20-31:8; 31:13-16; 33:13-19; 34:19-35:1; 38:19-39:17.) Dr. Wise further admitted that he stated, in an e-mail to Defendants' counsel on September 12, 2008, that he was not certain that he even presented the Wise poster at the New Orleans conference in 1987. (Wise Dep. Tr. 54:1-56:3.) That Dr. Wise, who serves as a paid consultant to Defendants in this litigation, lacks memory of whether and to what extent he may have distributed his own poster demonstrates that Defendants lack clear and convincing evidence of any public dissemination and thus warrants a finding that the Wise poster is not prior art. *See Lister*, 583 F.3d at 1317. ("Absent such evidence, we have no basis to conclude that the manuscript was publicly accessible prior to the critical date."); *Carella*, 804 F.2d at 139 (affirming finding of no "printed publication" status and hence no invalidity where evidence of public dissemination was lacking); *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1381 (Fed. Cir. 2008) (finding no error in the district court's finding that the Eastman Brochures were not printed publications, given the lack of evidence with regard to their distribution); *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1330 (Fed. Cir. 2004) (affirming the district court's holding that an IADR Abstract was not prior art because "there was not clear and convincing evidence that the Abstract was actually available at the IADR meeting").

4. Differences Between the Prior Art and the Claimed Subject Matter

As discussed above, the Court holds that one of ordinary skill in the art in October 1988 would not have chosen any carbostyril compound as a lead compound in an antipsychotic drug development

effort. Because each of Defendants' theories in support of their obviousness defense relies on a carbostyril compound as the lead compound, the Court concludes that each of these theories fails at the outset. The Court further concludes that, even if one of ordinary skill in the art in October 1988 would have been motivated to choose a carbostyril compound as a lead compound, Defendants have failed to prove that any of their proposed lead compounds would have been selected or that the prior art suggests the modification of these compounds to arrive at aripiprazole with a reasonable expectation of success.

a. The '528 Patent Claims Would Not Have Been Obvious Based on the 2,3-Dichloro Propoxy Compound

Defendants' primary argument in support of their obviousness defense is that the '528 patent claims would have been obvious in light of the prior art 2,3-dichloro propoxy compound. Defendants presented no testimony at trial in support of this theory of obviousness. In fact, Defendants' experts chose other lead compounds over the 2,3-dichloro propoxy compound, indicating that, in their opinion, one of ordinary skill in the art in October 1988 would not have chosen this compound as a lead compound. Defendants also presented no evidence as to why one of ordinary skill in the art would have modified this compound to arrive at aripiprazole with any reasonable expectation of success.

Defendants contend instead that the structural similarity between the 2,3-dichoro propoxy compound and aripiprazole renders aripiprazole *prima facie* obvious. Defendants urge that, because a prior art genus of compounds encompasses aripiprazole and other compounds claimed in the '528 patent, obviousness is judged in light of this structural similarity. The Court disagrees that this is a correct evaluation of the question of obviousness.

The Federal Circuit recently rejected a similar argument in *Daiichi,* 2010 U.S. App. LEXIS 18820. In *Daiichi*, the Defendant argued, as Defendants do here, that the district court should have chosen the structurally closest prior art compounds as the lead compounds in its obviousness analysis. U.S. App. LEXIS 18820 at *16. The Federal Circuit held, however, that the district court was correct in rejecting that argument, which it held ran "contrary to our caselaw." *Daiichi*, U.S. App. LEXIS 18820 at *16. The Federal Circuit further explained that "attribution of a compound as a lead compound after the fact must avoid hindsight bias." *Daiichi*, 2010 U.S. App. LEXIS 18820 at *16-17. In explaining the incorrectness of this obviousness argument based purely on structural similarity, the Court further cited to its prior decisions in *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369 (Fed. Cir. 2006) and *Takeda Chem. Indust. v. AlphaPharm Pty., Ltd.,* 492 F.3d 1350 (Fed. Cir. 2007). *Daiichi*, U.S. App. LEXIS 18820 at *16.

In *Eli Lilly*, which involved the antipsychotic drug olanzapine, the defendants had similarly claimed error in the district court's requirement that they establish some teaching or incentive in the prior art to choose the most structurally similar compound, the next adjacent homolog of olanzapine, as a lead compound. 471 F.3d at 1377. Moreover, in *Eli Lilly*, this prior art compound fell within a genus of compounds that had previously been patented by Eli Lilly in its prior art '574 patent. 471 F.3d at 1375. The Federal Circuit rejected this criticism by the defendants, holding that the district court had correctly found, among other things, that "a person of ordinary skill in the art would not have chosen [the asserted homolog compound] as the beginning compound . . . ." *Eli Lilly*, 471 F.3d at 1378-79. In *Takeda*, the court similarly upheld a district court's determination that the most structurally similar compound would not have been chosen as a lead compound. *Takeda*, 492 F.3d at 1356-60.

The Court is also unpersuaded by the other arguments Defendants assert in support of their obviousness theory based on the 2,3-dichloro propoxy compound. Defendants point to the reexamination prosecution history and note that the PTO ultimately concluded that the 2,3-dichloro compound was one of the closest prior art compounds. As noted above, however, structural similarity is not dispositive of the question of obviousness. Moreover, it is significant that the PTO never specifically cited to the 2,3-dichloro propoxy compound in support of any of its obviousness rejections.

Defendants further urge that various pieces of prior art, including the Nakagawa declaration, the SE '945 application and the Wise poster, would have led one of ordinary skill in the art to predict the properties of aripiprazole. For the reasons discussed above, the Court has found that antipsychotic drug discovery is inherently unpredictable and that the prior art references identified by Defendants do not render predictable aripiprazole's many unique and surprising properties.

The Court therefore concludes that the Defendants have not shown that claims 12, 17 and 23 would have been obvious in light of the 2,3-dichloro propoxy compound.

b. The '528 Patent Claims Would Not Have Been Obvious In Light of the Unsubstituted Butoxy Compound

Defendants' second argument in support of their obviousness defense relies on the unsubstituted butoxy compound as a lead compound. Defendants argue that one of ordinary skill in the art would have chosen the unsubstituted butoxy compound as a lead compound based upon the teachings of the Nakagawa declaration. As discussed above, even if one of ordinary skill in the art would have chosen a carbostyril compound as a lead compound and the Nakagawa declaration were available as prior art, there is no evidence that the Nakagawa declaration would have led one of ordinary skill in the art to choose the unsubstituted butoxy compound as a lead compound.

Defendants' expert Dr. Castagnoli opined that one of ordinary skill in the art would have chosen a different compound, OPC-4392, which was not included in the Nakagawa declaration. Another of Defendants' experts, Dr. Marshall, testified during his deposition that one of ordinary skill in the art would not have chosen a lead compound based on the Nakagawa declaration. [Tr. 688-90 (Marshall)] Dr. Press was the only witness who testified in support of the choice of the unsubstituted butoxy compound as a lead compound. Even Dr. Press acknowledged, however, that the purpose of the Nakagawa declaration was not to identify potential lead compounds for an antipsychotic research program. [Tr. 257 (Press)]

As discussed above, the Court finds that Otsuka's experts Dr. Roth and Dr. Nichols convincingly explained that one of ordinary skill in the art would not have used the Nakagawa declaration to choose a lead compound for development and, even if they did, they would not have chosen the unsubstituted butoxy compound. Instead they would have chosen compound 44, the most potent compound reported in the declaration. Compound 44 is structurally quite distinct from aripiprazole and would have led away from the structural features of aripiprazole.

As also discussed above, the Court concludes that Defendants have not shown that the prior art teaches the modifications necessary to convert the unsubstituted butoxy compound to aripiprazole. To the contrary, the prior art cited by Defendants taught away from disubstitution on the phenyl ring and had no clear teachings leading in the direction of aripiprazole with its unique 2,3-dichloro substituted phenyl ring. The Court further concludes that the art of antipsychotic drug discovery is inherently unpredictable and Otsuka showed that small chemical changes can lead to unpredictable changes in potency and potential to cause side effects. Accordingly, Defendants have not carried their burden of showing that one of ordinary skill in the art in October 1988 would have had any reasonable

expectation of success with respect to any of the proposed modifications of the unsubstituted butoxy compound.

The Court concludes that claims 12, 17 and 23 of the '528 patent would not have been obvious in light of the unsubstituted butoxy compound.

c. The '528 Patent Claims Would Not Have Been Obvious In Light of OPC-4392

Defendants' final argument in support of their obviousness defense is that the '528 patent claims are obvious in light of OPC-4392. As discussed above, even if one of ordinary skill in the art in October 1988 were to choose a carbostyril compound as a lead compound in an antipsychotic drug development effort, they would not have chosen OPC-4392. Defendants presented little evidence in support of this choice of compound and the evidence weighs heavily against choosing a compound such as OPC-4392 that failed in clinical trials.

Dr. Castagnoli was the only testifying expert witness who selected OPC-4392 as a lead compound. Dr. Press, Defendants' other testifying expert who opined on obviousness, did not choose OPC-4392 as a lead compound. Moreover, as discussed above, the Court finds that Dr. Castagnoli lacked the expertise in analyzing clinical study results to fully appreciate the prior art reports concerning OPC-4392. As Dr. Roth convincingly explained, these prior art reports indicated that OPC-4392 lacked antipsychotic efficacy and further exhibited potentially dangerous side effects. One of ordinary skill in the art in October 1988 would not have chosen such a compound as a lead compound.

As also discussed above, the Court concludes Defendants have not shown that the prior art teaches the modifications necessary to convert OPC-4392 to aripiprazole. To the contrary, the prior

art cited by Defendants, taught away from disubstitution on the phenyl ring. To the extent the Wise poster is considered prior art, it taught away from the use of any substituents on the phenyl ring. The prior art also failed to suggest the other unique structural features of aripiprazole, including its butoxy linker. Moreover, while Defendants attempt to rely on generalized teachings in the prior art concerning homologs, the Court disagrees that these teachings lead toward aripiprazole. The Court further disagrees that the prior art supports Defendants' theory of "routine optimization." Dr. Castagnoli was the only expert to espouse this approach to antipsychotic research and he has never personally conducted this type of research. The Court concludes that Otsuka convincingly showed that antipsychotic drug discovery is inherently unpredictable and there is nothing routine about it. Accordingly, Defendants have not carried their burden of showing that one of ordinary skill in the art in October 1988 would have had any reasonable expectation of success with respect to any of the proposed modifications of the OPC-4392.

The Court concludes that claims 12, 17 and 23 of the '528 patent would not have been obvious in light of OPC-4392.

5. Objective Evidence Independently Establishes that Aripiprazole Would Not Have Been Obvious

Defendants have not established a *prima facie* case of obviousness. Even if they had, however, there is overwhelming objective evidence of nonobviousness in this instance to overcome such a *prima facie* case.

Any obviousness analysis requires a Court to examine objective evidence of nonobviousness (sometimes referred to as secondary factors). *Janssen*, 456 F. Supp. 2d at 669. Objective evidence of nonobviousness "may often be the most probative and cogent evidence in the record" and, indeed,

secondary considerations "may be sufficient to overcome a *prima facie* case of obviousness." *Id*. Objective evidence "is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness." *Ortho-McNeil*, 520 F.3d at 1365.

Such objective evidence of nonobviousness includes, *inter alia*, long-felt but unmet need, failures of others, commercial success, copying, unexpected results, and industry acclaim. *Graham*, 383 U.S. at 17-18. The rationale for giving weight to these so-called "secondary factors" is that "they provide objective evidence of how the patented product is viewed in the marketplace, by those directly interested in the product." *Demaco Corp. v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988). Secondary considerations extend beyond what was known at the time of the invention and may include later discovered unexpected properties of the invention. *Daiichi Sankyo Co., Ltd. v. Mylan Pharms.*, 670 F. Supp. 2d 359, 381 (D.N.J. July 30, 2009), *aff'd*, 2010 U.S. App. LEXIS 18820 (Fed. Cir. Sept. 9, 2010). In this case, each of the secondary factors of (a) long-felt but unmet need, (b) failures of others, © commercial success, (d) copying, (e) unexpected results, and (f) industry acclaim weighs in favor of a finding of nonobviousness.

a. Long-Felt but Unmet Need

As described above in Section III.D, as of 1988, there was a long-standing medical need for an improved antipsychotic drug that could treat the positive symptoms of schizophrenia with reduced side effects. All antipsychotics marketed in the United States in 1988 were first-generation typical antipsychotics such as haloperidol and chlorpromazine, which treated the positive symptoms of schizophrenia but still caused serious side effects such as EPS and tardive dyskinesia (TD). The second-generation antipsychotics Defendants point to in an effort to challenge Otsuka's evidence of

long-felt need were not available to patients in October 1988, the relevant date for assessing long-felt need.

Defendants have not raised any serious challenge to the long-felt but unmet need in October 1988 for an improved antipsychotic drug. As this Court previously found, it is "undisputed that there was a long-felt but unsolved need for a safe, atypical antipsychotic that did not cause EPS or TD from at least the 1960s until 1985 and beyond." *Janssen*, 456 F. Supp. 2d at 670. This long-felt need, which was met by aripiprazole, demonstrates the nonobviousness of claims 12, 17 and 23 of the '528 patent.

Defendants contend that the evidence of long felt but unmet need is not relevant to nonobviousness because of the existence of Otsuka's '416 "blocking" patent, which they alleged prevented others from addressing the long felt need before Otsuka. In fact, Defendants raise this same argument for all of Otsuka's evidence of secondary indica of nonobviousness. As discussed below in Section VI.A.5.d, Defendants have not proven that the alleged blocking patent in fact blocked any others from doing research in this area.

In fact, the evidence of record demonstrates that the '416 patent did not act to block research in this area, and, in particular, did not act to block research concerning aripiprazole. For example, Defendant Teva filed numerous patent applications directed to crystalline forms of aripiprazole while the '416 patent was still in force. [PTX 612, 613, 620, 624, 625, 659]

b. Failure of Others

As discussed above in Section III.D, researchers attempted for years to create an improved antipsychotic that would treat the positive symptoms of schizophrenia without causing EPS, TD, or other adverse effects such as agranulocytosis. Those efforts largely failed, as reflected, for example,

by the fact that the FDA did not approve a single new antipsychotic drug from about 1976 to 1989. [Tr. 1134-1136 (Roth); Tr. 1565 (Nichols); PTX 79] *See also Janssen*, 456 F. Supp. 2d at 670 (finding that there was a failure to develop a safe atypical antipsychotic). These widespread failures further establish the nonobviousness of claims 12, 17 and 23 of the '528 patent.

c. Commercial Success

Commercial success is "usually shown by significant sales in a relevant market." *Neupak, Inc. v. Ideal Mfg. & Sales Corp.*, 41 Fed. Appx. 435, 440 (Fed. Cir. 2002). Evidence of an invention's commercial success "may present strong evidence of non-obviousness." *Daiichi*, 670 F. Supp. 2d at 384. In order to support a finding of commercial success, there must be a sufficient relationship between the commercial success and the patented invention (often referred to as a "nexus" between the commercial success and the patented invention), such that the objective evidence should be considered in the determination of nonobviousness. *Demaco*, 851 F.2d at 1392. The burden of proof as to this connection or nexus resides with the patentee. *Id*. "A *prima facie* case of nexus is generally made out when the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent." *Id*.

The patent need not be the only reason for the commercial success of a patented invention, and "a patentee is not required to prove as part of its prima facie case that the commercial success of the patented invention is not due to factors other than the patented invention." *Id.* at 1394. *See also Continental Can. Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991) ("[i]t is not necessary...that the patented invention be solely responsible for the commercial success, in order for this factor to be given weight appropriate to the evidence, along with other pertinent factors.")

When the patentee has presented a *prima facie* case of nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger, as in any civil litigation. *Demaco*, 851 F.2d at 1393. Mere argument is insufficient to rebut such a *prima facie* case, and it is the task of the challenger to "adduce evidence" to show that the commercial success was not due to the patented invention. *Id.* In this case, as discussed above in Section IV.J.3, Otsuka has shown a clear relationship between the commercial product, Abilify®, and the invention of the '528 patent. The asserted claims of the '528 patent cover the molecule that is known as aripiprazole, chemical compositions that include aripiprazole, and methods to use aripiprazole in the treatment of schizophrenia in a patient. [PTX 1; Tr. 2003 (Jarosz)] Aripiprazole is the active ingredient in the pharmaceutical product currently available in the United States under the trade name of Abilify®, which is sold in the United States by Otsuka and BMS. [Tr. 2003-4 (Jarosz)] Thus, Abilify® is a direct product manifestation of the '528 patented invention, and a clear nexus between the patent and the commercial product has been demonstrated.

Otsuka has also shown that Abilify® achieved a great deal of commercial success. That commercial success is demonstrated by the substantial payments by BMS to Otsuka for rights to co-market Abilify® as well as substantial and growing commercial sales of Abilify®. By the end of 2009, sales of Abilify® were $3.3 billion on an annual basis. The total U.S. sales of Abilify® by Otsuka and BMS, through all distribution channels, have been $12.5 billion from its introduction in November of 2002 through February of 2010. From 2005 onward, sales of Abilify® exceeded a billion dollars each year, qualifying it as a "blockbuster drug." [PTX 347, PTX 348, PTX 372, PTX 385, PTX 386, and PTX 775; Tr. 2020-2022 (Jarosz)]

Otsuka further demonstrated that Abilify® has been widely prescribed and that Abilify® has been extremely successful when compared to the other products in its relevant market. [PTX 349 - PTX 353; PTX 386 - PTX 388; Tr. 2029-30 (Jarosz)] In 2009, Abilify® was the second largest selling atypical antipsychotic, behind only Seroquel, and the sixth most successful prescription drug in the United States (as measured in dollar sales). [PTX 776; PTX 777; Tr. 2032 (Jarosz)] Abilify® is also one of the most successful products introduced in the industry in the last few years, when compared to the quarterly sales performance of other compounds that were launched. [PTX 374; Tr. 2038 (Jarosz)] When compared to other top pharmaceutical product launches, including the launches of Advair, Avandia, Celebrex, Lipitor, Nexium, Rezulin, Viagra, Vioxx, and Zyprexa, Abilify® is in the top seven product launches in industry history. [PTX 781; Tr. 2039 (Jarosz)] Abilify® has been BMS's second largest blockbuster drug to date. [PTX 782; Tr. 2037-2038 (Jarosz)]

Otsuka additionally showed that the benefits and advantages of the '528 patent have been the primary drivers of Abilify®'s commercial success, not other factors such as marketing or pricing. [Tr. 2063-73 (Jarosz)]

(1) Defendants Have Failed to Rebut the Showing of Commercial Success

Defendants contend that the commercial success of aripiprazole is not relevant to nonobviousness because of the existence of Otsuka's '416 "blocking" patent, citing to *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). This argument misstates the holding in *Merck* and fails to account for significant factual differences between Merck and the present case. Defendants also have failed to show that the '416 patent in fact acted as a blocking patent.

In *Merck*, the Federal Circuit determined that, under the facts present in that case, the evidence of commercial success was "not significantly probative." 395 F.3d at 1377. Thus, the Court did not find the evidence irrelevant, as Defendants contend. The Court merely found this evidence of limited weight.

Moreover, *Merck* did not concern the nonobviousness of claims directed to a new chemical compound, such as the claims in the present case. Instead, *Merck* involved a patent that disclosed a method of treating osteoporosis through less-than-daily administration of certain bisphonate compounds, which included the FDA-approved drug Fosomax. 395 F.3d at 1366. The closest prior art, as determined by the court, was a quarterly news letter that also taught the less-than-daily ("once-weekly") administration of Fosomax. *Merck*, 395 F.3d at 1368. In that case, because of Merck's prior patents and FDA exclusivity to offer Fosomax, the court found that the author of the news quarterly was not able to put his idea into practice, even if he had wanted to. *Merck*, 395 F.3d at 1377. In other words, the prior art specifically taught a method that was blocked from coming to market, which method the court concluded could have significantly impacted the commercial success of the patent at issue. The facts here are quite different and therefore *Merck* is inapposite.

The facts in this case are more analogous to those in *Takeda Chemical Industries, Ltd v. Mylan Laboratories, Inc.*, 417 F. Supp. 2d 341 (S.D. N.Y. 2006), *aff'd*, 549 F.3d 1381 (Fed. Cir. 2008), where the court rejected the same exact argument that defendants are attempting to make here (also relying on *Merck*) as "specious." *Takeda*, 417 F. Supp. 2d at 387 ("Alphapharm has not shown that any of the compounds disclosed by Takeda in its patents were viable candidates for commercial development. Takeda's competitors had every opportunity to develop compounds that were improvements over the compounds Takeda disclosed.".

Defendants also have not proven, as was found in *Merck*, that the alleged blocking patent, the '416 patent, in fact blocked any others from doing research in this area. Defendants have presented no evidence that any competitor ever refrained from developing aripiprazole or other carbostyril derivatives due to concerns about any "blocking" patent owned by Otsuka. Moreover, as discussed above in Section IV.J.3.a, Defendants also have no expert testimony to support this speculative theory and instead rely on unsupported anecdotes and attorney argument. Such conjecture is insufficient to rebut the *prima facie* case of nexus established by Otsuka. *See Demaco*, 851 F.2d at 1393 ("It is thus the task of the challenger to adduce evidence to show that the commercial success was due to factors other than the patented invention.").

The evidence of record also demonstrates that the '416 patent did not block research in this area, and, in particular, did not block research concerning aripiprazole. Defendant Teva filed numerous patent applications directed to crystalline forms of aripiprazole while the '416 patent was still in force. [PTX 612, 613, 620, 624, 625, 659] This evidence directly contradicts Defendants' blocking patent argument.

Defendants point out that these patent applications were not filed until after aripiprazole was approved by the FDA in November 2002. This argument, however, is beside the point. Either the '416 patent in fact blocked research in this area or it did not. Defendants' patenting activity indicates it did not and Defendants have identified no specific evidence to the contrary.

Finally, Defendants point to other factors that they contend negate Abilify®'s commercial success. Defendants improperly point to the fact that Otsuka and BMS paid fines to the Department of Justice and District of Massachusetts in settlement of claims that Otsuka and BMS improperly marketed Abilify® . Defendants do not explain why such settlements affect either the commercial

success of Abilify® or the nexus between the commercial success of Abilify® and the '528 patent. Furthermore, in *Daiichi*, similar allegations from the FDA of "false and misleading promotional materials" did not alter the Court's finding of nexus or commercial in that case, particularly where, as here, the sales of the product continued to increase after the allegedly improper marketing ceased. 670 F. Supp. 2d at 386. [PTX 385; PTX 775]. The Court therefore rejects and disregards this argument by Defendants.

Defendants also point to the '416 patent and contend that some of Abilify®'s commercial success must be due to this patent. Defendants make no effort, however, to quantify how the '416 patent detracts from Abilify®'s commercial success, in their view, nor do they contend that it affects the nexus between Abilify®'s success and the '528 patent claims. Nor do Defendants explain how the '416 patent can be responsible for the commercial success of a product based on a compound that is not disclosed in the '416 patent. Moreover, as noted previously, Otsuka need not prove that the '528 patent is the only reason for the commercial success of Abilify®. *Demaco*, 851 F.2d at 1394; *Continental Can*, 948 F.2d at 1273. The Court therefore rejects this unexplained and unsubstantiated argument.

As such, Otsuka demonstrated the substantial commercial success of Abilify® and Defendants have failed to rebut the evidence of that commercial success or the nexus of that success to the benefits and advantages of the '528 patent. This commercial success supports the nonobviousness of claims 12, 17 and 23 of the '528 patent.

d. Copying

As discussed above in Section IV.J.4, the evidence shows substantial copying of the invention of the '528 patent by Defendants through their ANDA filings at issue in this litigation and also through

their patenting activities directed to aripiprazole. Defendants' copying of Otsuka's aripiprazole invention is further objective evidence supporting this Court's conclusion that the asserted '528 patent claims would not have been obvious.

Defendants contend in response that copying is not compelling evidence of nonobviousness in the ANDA context. [Def. FOFCOL, pages 133-34] Defendants' blanket assertion is too broadly framed, however, and the cases Defendants cite for support are distinguishable in that the patent claims in those cases did not cover the active pharmaceutical ingredient. *See*, *e.g.*, *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, Nos. 2009-1553, -1592, 2010 U.S. App. LEXIS 11246, at *1 (Fed. Cir. June 3, 2010) (claims directed to "formulations suitable for once daily oral dosing"). Where the asserted claims are directed to the active pharmaceutical ingredient, as in the present case, copying has been found to be important evidence of nonobviousness in the ANDA context. *See Forest Labs., Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 496 (D. Del. 2006), *aff'd*, 501 F.3d 1263, 1267, 1269 (Fed. Cir. 2007).

Specifically, the district court in *Forest Labs.* found, and the Federal Circuit agreed, that copying compelled a conclusion of nonobviousness because of the impressive number of generic drug companies who filed ANDA applications, and the fact that some of those generic drug companies still filed ANDA applications although they already were selling products directed to the same indication as the ANDA applications at issue in the case. *See id.* This reasoning applies equally well here. At least seven different generic drug companies have filed ANDA applications to various aripiprazole products, including aripiprazole tablets, aripiprazole orally disintegrating tables, and aripiprazole oral solutions. *See* Pretrial Order at pages 6-8, 10-11. The fact that these generic drug companies *chose* to copy aripiprazole so that they can file their respective ANDAs speaks to the unique mechanism of

action of aripiprazole compared to other atypical antipsychotics, and consequently, aripiprazole's impressive safety and pharmacological profiles, and aripiprazole's commercial success. [Tr. 2004, 2021, 2058-2059, 2062 (Jarosz)]

Defendants additionally argue that copying is of no import in this case because copying in the ANDA context does not justify making the "inference that it seeks to draw," which is "that the technical challenges were so great that success was beyond the reach of those of ordinary skill in the art." [DEF. FOLCOL, page 134] Defendants do not cite any case law for this proposition and therefore this argument is hardly credible. The unrebutted evidence also establishes that antipsychotic drug discovery is enormously difficult, fully justifying the inference that technical challenges in this area cause Defendants to copy Otsuka's patented technology rather than develop their own.

Finally, Defendants ignore that in the present case, copying extends far beyond the ANDA applications. Defendants and other generic drug companies have additionally made and used aripiprazole in developing various aripiprazole crystalline forms and related technologies, for which they have pursued patent protection. [*See* PTX 612; PTX 613; PTX 659].

The Court concludes that this evidence of extensive copying by Defendants further supports the nonobviousness of claims 12, 17 and 23 of the '528 patent.

e. Unexpected Results

As established above, aripiprazole has a number of unexpected therapeutic benefits as a partial dopamine agonist, including its broad efficacy in treating the positive symptoms of schizophrenia and favorable side-effect profile, e.g., causing reduced or no EPS, TD, sedation, weight gain or other metabolic effects, prolactin elevation, or orthostatic hypotension. The drug's therapeutic benefits and side-effect profile could not have been predicted in 1988.

Aripiprazole has been approved for several indications in addition to the treatment of schizophrenia, including as an add-on treatment for major depressive disorders, for acute and maintenance treatment of adults with manic or mixed episodes associated with Bipolar I Disorder, for the acute treatment of pediatric patients 10 to 17 years of age with manic or mixed episodes associated with Bipolar I Disorder, and for the treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years of age. Aripiprazole's efficacy in treating those medical conditions would have been completely unexpected to a person of ordinary skill in 1988.

As discussed in detail in Section IV.J.5.b, aripiprazole also exhibits unexpectedly favorable test results in animal test models. For example, aripiprazole exhibits unexpectedly greater potency in the stereotypy test than each of the specific prior art carbostyril derivatives that Defendants have identified as lead compounds in their obviousness analysis. Data reported in an article published by Otsuka in 1998 showed that the unsubstituted butoxy compound was inactive in the stereotypy test up to the highest dosage tested. [Tr. 1229-32; 1239-40 (Roth); PTX 564 at 661 (compound no. 4)] This same article also reported that OPC-4392 (compound no. 1) showed very low potency in the stereotypy test, consistent with Dr. Oshiro's observations during his research leading to the discovery of aripiprazole that OPC-4392 showed low potency in this test and therefore was ineffective in treating the positive symptoms of schizophrenia [PTX 564 at 661; Tr.1754; 1768-69 (Oshiro)]

As for the third lead compound identified by Defendants, the 2,3-dichloro substituted propoxy compound, this compound was tested and directly compared to aripiprazole in Dr. Hirose's declaration. As discussed above in Section IV.J.5.b.(1), the Hirose declaration test data show the unexpected superiority of aripiprazole in the stereotypy test and in the B-over-A therapeutic ratio comparing the anti-epinephrine and stereotypy test results.

Defendants have failed to rebut this showing of unexpected results. Defendants contend that the unexpected properties of aripiprazole are not relevant to nonobviousness because of the existence of Otsuka's '416 "blocking" patent, which they assert may have discouraged others from working in the carbostyril derivative field. However, as explained above in Section IV.J.5.b.(2) above, Defendants have presented no evidence in support of this position. Moreover, nothing in Defendants argument addresses why the '416 patent would have made any of the properties of aripiprazole any more expected.

The unexpectedly superior properties of aripiprazole further establish the nonobviousness of claims 12, 17 and 23 of the '528 patent.

f. Industry Acclaim

Abilify® has also achieved substantial industry acclaim, which acclaim is further evidence of the nonobviousness of the claims of the '528 patent. *Graham*, 383 U.S. at 17-18.

Abilify® has won a number of awards throughout the world over the years. Among those awards, Abilify® won the 2004 Frost & Sullivan Product Innovation Award for the U.S. antipsychotic medications market, the prestigious Prix Galien award in 2006 (France) for being the most innovative pharmaceutical product on the market, the Pharmaceutical Executive Magazine Central Nervous System Compound of the Year for 2004 (US), and a variety of other awards in Germany, Japan, France and Spain. [PTX-375; Tr. 2042-4 (Jarosz)] Each of these awards is evidence of the acclaim that aripiprazole has received in the industry and supports the nonobviousness of claims 12, 17 and 23 of the '528 patent.

Defendants have failed to rebut this showing of industry acclaim. Defendants allege that the awards given to Otsuka for Abilify® "were presumably for the entire research effort made by Otsuka,"

including "Otsuka's own work that is citable as prior art, such as OPC-4392 and the Nakagawa Declaration." Defendants provide no support for this position. To the contrary, the awards and acclaim garnered by Otsuka for Abilify® certainly were not for Otsuka's failed OPC-4392 compound, but instead for the great success of Abilify®. In particular, Frost & Sullivan described their Product Innovation Award for the U.S. antipsychotic medications market to Otsuka for Abilify® as being "bestowed on the company that successfully develops and commercializes a medication which is believed to provide a unique set of benefits over existing products in the market." [PTX 357; Tr. 2042 (Jarosz)] In its report covering the award, Frost and Sullivan stated: "With a comparable efficacy and superior side effect profile, Abilify® may become the new standard against which all new antipsychotics are judged." [PTX 357; Tr. 2044 (Jarosz)] Frost & Sullivan did not say anything about the award being bestowed upon Otsuka for its work on the failed OPC-4392 compound. The evidence shows that the other awards garnered by Otsuka were also for Abilify®, and not for its past failures. *See, e.g.*, PTX 375.

B. Defendants' Double Patenting Defense

1. Legal Standards for Non-Statutory Double Patenting

Non-statutory, or "obviousness-type," double patenting is a judicially created doctrine adopted to prevent claims in separate applications or patents that do not recite the "same" invention, but nonetheless claim inventions that are not patentably distinct. *See, e.g., General Foods Corp. v. Studiengesellschaft Kohl mbH*, 972 F.2d 1272, 1279-80 (Fed. Cir. 1992); *In re Metoprolol Succinate Patent Litigation*, 494 F.3d 1011, 1016 (Fed. Cir. 2007). A non-statutory double patenting analysis involves the comparison of a claim in an earlier patent to a claim in a later commonly owned patent, and a determination of the differences in subject matter between the two claims. If those differences

do not render the claims patentably distinct, the later claim is invalid for non-statutory double patenting. "A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Metoprolol*, 494 F.3d at 1016.

A non-statutory double patenting inquiry does not consider the specification of the earlier patent, but merely compares the earlier claims to the claims in the later patent. *General Foods*, 972 F.3d at 1281-82. Historically, double patenting has been raised as a validity challenge when the patent containing the earlier claims is not available as prior art. *See, e.g., In re Ornitz*, 376 F.2d 330, 334 (C.C.P.A. 1967) (noting that the PTO issues double patenting rejections when "the reference relied on is not 'prior art'")

When the earlier patent is available as prior art, however, the full disclosure of the earlier patent may be considered in an obviousness analysis under § 103. Under these circumstances, any double patenting inquiry is subsumed by that broader inquiry under 35 U.S.C. § 103, which considers the full patent disclosure of that earlier patent, including the claims. There is therefore no need to conduct a separate double patenting analysis. *See, e.g., Sanofi-Synthelabo*, 492 F. Supp. 2d at 393. ("The double-patenting inquiry is subsumed by the broader statutory inquiry pursuant to 35 U.S.C. § 103 because Sanofi's entire '596 patent was prior art at the time the '265 patent issued."), *aff'd*, 550 F.3d 1075 (Fed. Cir. 2008); *In re Jezl*, 396 F.2d 1009, 1013 (C.C.P.A. 1968) ("The view we take renders it unnecessary to consider at length the double patenting rejection advanced by the board."); *Ornitz,* 376 F.2d at 334 ("Where it is possible to conduct the broader inquiry permitted by sections 102(e) and 103 because the references are 'prior art,' it does not make sense to resort to the narrower inquiry which underlies a 'double patenting' rejection."); *In re Land*, 368 F.2d 866, 884 (C.C.P.A. 1966) ("As

to the claims on which we have reversed the obviousness rejection, *a fortiori* this double patenting rejection, predicated on obviousness, would be reversed for the same reasons.").

In the present case, the '416 patent is available as prior art. Accordingly, any double patenting inquiry premised on the '416 patent claims is subsumed by the broader inquiry under § 103, and it is therefore unnecessary to separately consider the issue of double patenting.

Defendants do not address or distinguish this case law or otherwise explain why their double patenting challenge is not subsumed by the broader obviousness inquiry under § 103. Defendants nevertheless contend that the legal analysis in a double patenting challenge differs from that of an obviousness analysis under § 103, relying on *Geneva Pharms., Inc.v. Glaxosmithkline P.L.C.*, 349 F.3d 1373, 1377-78 (Fed. Cir. 2003). The facts of *Geneva* are distinguishable, however, from the facts of the present case.

In *Geneva*, the Federal Circuit considered a double patenting allegation where the later claims were *anticipated* by the prior claims. *Geneva Pharms*., 349 F.3d at 1384 ("This genus-species relationship makes the claims patentably indistinct, because an earlier species within the Crowly claim anticipates the later genus of the '352 and '552 claims"); *see also Metoprolol*, 494 F.3d at 1016 (holding that, in a non-statutory double patenting analysis, "[a] later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or *anticipated* by, the earlier claim." (emphasis added)). Given these facts underlying the *Geneva* Court's double patenting analysis, the Court explained that the legal analysis underlying non-statutory or "obviousness-type" double patenting may differ from an obviousness analysis under 35 U.S.C. § 103. *Geneva Pharms.,* 349 F.3d at 1377-78 (noting that a double patenting inquiry does not require inquiry into motivation to modify the prior art or inquiry into objective criteria suggesting nonobviousness). Because the *Geneva* Court's

legal analysis underlying its double patenting inquiry was an anticipation analysis, the issues of motivation to modify the prior art and objective indicia of nonobviousness were not relevant to the inquiry.

Where the double patenting inquiry involves, however, a determination of whether the later claims are obvious in light of the subject matter of the prior claims, a full obviousness analysis under 35 U.S.C. § 103 is the appropriate legal analysis, including all of the factors set forth in *Graham*, 383 U.S. 1. As explained in the PTO's Manual of Patent Examining Procedures ("M.P.E.P."):

> A double patenting rejection of the obviousness-type, if not based on an anticipation rationale, is 'analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103' except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967) . . . [T]he factual inquiries set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103 are employed when making an obvious-type double patenting analysis.

M.P.E.P 804(II)(B)(1). Several district courts have reached this same conclusion. *See, e.g., Eli Lilly Co. v. Zenith Goldline Pharms., Inc*., 364 F. Supp. 2d 820, 910-12 (S.D. Indiana 2005), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006); *In re Glaxo '845 Patent Litig.*, 450 F. Supp.2d 435, 438 (S.D.N.Y. 2006); *Pfizer Inc.v. Synthon Holdings BV*, 2006 WL 2553370 *21 (M.D.N.C. Aug. 31, 2006), rev'd on other grounds in *Pfizer Inc.v. Synthon Holdings BV*, 2007 WL 1800165 (Fed. Cir. June 5, 2007).

The Federal Circuit and its predecessor Court also have repeatedly acknowledged the appropriateness of considering evidence of motivation to combine and objective indicia of nonobviousness in a double patenting analysis under these circumstances. *See Ortho Pharmaceutical Co. v. Johnson & Johnson Corp.*, 959 F.2d 936, 943 ("Given the structure and properties of the components claimed in '081 and '909, there would have been no suggestion in the art (and, hence, it

would not have been obvious) to modify those structures in order to achieve the compounds of [the patent-in-suit].'"); *see also In re Baird,* 348 F.2d 974, 979 (C.C.P.A. 1965) ("This [double-patenting] problem may also be stated to be whether it would have been obvious to one of ordinary skill to modify the process the patent claims by eliminating the irradiation step."); *In re Emert*, 124 F.3d 1458, 1462 (Fed. Cir. 1997) ("Absent some indication of unexpected properties, the [patented] combination rendered [the claimed invention] obvious [for double patenting]."); *In re Longi*, 759 F.2d 887, 896 ("[W]e must look to the Albizatti declaration [purporting to outline unexpected results] to determine whether the Board correctly concluded that this sole rebuttal evidence was insufficient to overcome the *prima facie* case.").

Because the double patenting challenge in the present case involves an allegation that the '528 patent claims are obvious in light of certain '416 patent claims, this case does not present the type of situation addressed in *Geneva*. Accordingly, the Court does not agree that *Geneva* requires a departure from the standard obviousness analysis under 35 U.S.C. § 103 in assessing Defendants' double patenting claims. This Court holds that the double patenting analysis is properly subsumed within the obviousness analysis based upon the '416 patent.

Finally, the Court also notes that Defendants repeatedly, and incorrectly, argue that Otsuka patented aripiprazole twice, suggesting that Otsuka's earlier genus claims in the '416 patent render the claims covering aripiprazole invalid. This is not a correct statement of the law of double patenting. While the doctrine of double patenting is intended to prevent the unjustified extension of patent rights, there is no unjustified extension when the patented invention is not obvious. *See In re Braat*, 937 F.2d 589, 594-95 (Fed. Cir. 1991) ("[o]nly if the extension of patent right is unjustified is a double patenting rejection appropriate. There are situations where the extension is justified. This case presents such

a situation.") Moreover, the fact than an earlier patent claim may dominate and encompass a later patent claim does not render the later claim invalid for double patenting. So long as the later patent claim is novel and nonobvious in light of the prior art, it can co-exist with an earlier-expiring dominant patent claim and "domination is an irrelevant fact." *In re Kaplan*, 789 F.2d 1574, 1578 (Fed. Cir. 1986); *see also Eli Lilly*, 364 F. Supp. 2d at 910-11 (rejecting argument that earlier dominating patent claims render later narrower claims invalid).

2. The '528 Patent Claims Are Not Invalid for Double Patenting Over Claim 13 of the '416 patent

Because the Court has determined that claims 12, 17 and 23 are nonobvious in light of the '416 patent, as discussed above, it need not separately address the narrower issue of whether these patent claims are nonobvious in light of claim 13 of the '416 patent. Nevertheless, the Court concludes there is in fact no double patenting based on claim 13 of the '416 patent. Defendants have not shown that one of ordinary skill in the art would have chosen the compound of claim 13 to modify to create an improved antipsychotic drug. Defendants also have not shown that, even assuming one of ordinary skill in the art would have chosen the compound of claim 13, that it would have been obvious to modify this compound to create aripiprazole.

a. One of Ordinary Skill in the Art Would Not Have Chosen The Compound of Claim 13 as a Lead Compound

Defendants contend that, in a double patenting analysis, they need not show that one of ordinary skill in the art would have chosen the claimed compound as a lead compound in an antipsychotic drug development effort. Defendants contend, without support, that the patentee has already "selected its 'lead compounds' by choosing to claim them in the earlier patent." [Def. FOFCOL, page 91] The Court does not accept this argument.

Defendants' arguments that aripiprazole is an obvious modification of the compound of claim 13 are based on references that Defendants contend relate to antipsychotic drugs. This prior art is only relevant to the potential modification of the compound of claim 13 to the extent one of ordinary skill in the art would seek to modify the compound of claim 13 to create an improved antipsychotic drug. In addition, the '528 patent claims at issue here include, in addition to claim 12 directed to the compound aripiprazole, claim 17 directed to a pharmaceutical composition for treating schizophrenia containing aripiprazole, and claim 23 directed to a method for treating schizophrenia by administering a composition containing aripiprazole. Defendants must show, in a double patenting analysis, that each of the '528 patent claims would have been obvious in light of claim 13 of the '416 patent, including claims 17 and 23, which are generally directed to the treatment of schizophrenia. Thus, taking into account the claims at issue as well as Defendants' specific arguments that these claims would have been obvious, the Court concludes that Defendants must first show that one of ordinary skill in the art would choose the compound of claim 13 as a starting point to modify to create an improved antipsychotic drug.

As discussed above in Section IV.E, one of ordinary skill in the art never would have chosen any compound in the '416 patent as a lead compound. There is nothing in the '416 patent that identifies the compound of claim 13, the unsubstituted butoxy compound, as an antipsychotic. Indeed, it is undisputed there is no information in the '416 patent that would have allowed a person of ordinary skill in the art in October 1988 to determine which carbostyril derivatives, if any, are antipsychotics. [Tr. 1220 (Roth); Tr. 228-229 (Press)]

In addition, it is undisputed that the claims of the '416 patent specifically describe the unsubstituted butoxy compound as an antihistaminic agent. [Tr. 1222-1224 (Roth); Tr. 1631

(Nichols); Tr. 240-241 (Press)] The claims specifically directed to a central nervous controlling effect exclude the unsubstituted butoxy compound from their scope because they are limited to 6-position isomers with a propoxy linker whereas the unsubstituted butoxy compound is a 7-position isomer with a butoxy linker. [Tr. 1632-1634 (Nichols); Tr. 243-245 (Press)]

A person of ordinary skill in the art in October 1988 would not have selected an antihistamine such as the unsubstituted butoxy compound as a lead compound for antipsychotic drug discovery. [Tr. 1631 (Nichols); Tr. 1386-1389 (Roth)] Instead, they would have selected as a lead compound some molecule that had antipsychotic activity in an animal or a preclinical model. [Tr. 1632 (Nichols)]

The Nakagawa declaration, the only other prior art document Defendants discuss in their double patenting analysis, also does not provide a reason for one of ordinary skill in the art to choose the unsubstituted butoxy compound as lead compound in antipsychotic drug development. [Def. FOFCOL, pages 92-96] As discussed above, a person of ordinary skill in the art would have given little weight to the mouse jumping data reported in the Nakagawa declaration.

Those data, moreover, would not have motivated one of ordinary skill in the art to choose the unsubstituted butoxy compound to modify to generate a potential antipsychotic. The most potent compound in the Nakagawa declaration, compound 44, was a propoxy-linked compound, not a butoxy-linked compound, and further was a 5-position isomer, not a 7-position isomer like the unsubstituted butoxy compound. [Tr. 1638-45 (Nichols)] One of ordinary skill in the art relying on the Nakagawa mouse jumping data would have been motivated to choose, if anything, the structurally distinct compound 44, not the unsubstituted butoxy compound.

For the foregoing reasons, and also for the reasons discussed above in Sections IV.E and IV.F, the Court finds that it would not have been obvious for one of ordinary skill in the art to choose the compound of claim 13 and attempt to modify it to obtain an improved antipsychotic drug.

b. The Prior Art Does Not Teach Modification of the Compound of Claim 13 to Arrive at Aripiprazole

Even if one of ordinary skill in the art would have chosen the compound of claim 13 and sought to modify it to create an improved antipsychotic, the prior art does not suggest the specific modifications necessary to arrive at aripiprazole. Tellingly, Defendants' expert Dr. Castagnoli testified that one of skill in the art would be motivated to add *methyl* groups to the unsubstituted butoxy compound [Tr. 757-58 (Castagnoli)] directly contradicting Dr. Press's testimony that one would seek to chlorinate this compound. [Tr. 127 (Press)] According to Dr. Castagnoli: "the teachings which I consider to be loud and clear are the following: from the unsubstituted [butoxy compound], you want to incorporate the characteristics of [OPC] 4392 because of its known activity in humans. So put the 2,3,-dimethyl group on there would give rise to a 4392 type molecule . . . ." [Tr. 757-58 (Castagnoli)]

In support of their double patenting argument for modifying the unsubstituted butoxy compound, Defendants rely on the '416 patent and the Nakagawa declaration. For the reasons discussed above, these documents do not suggest modifying the unsubstituted butoxy compound to arrive at aripiprazole. Among other things, the '416 patent teaches away from a 2,3-dichloro substitution pattern in that it does not contain a single example of a 2,3-dichloro substituted compound. [Tr. 1624-25 (Nichols); Tr. 231 (Press); DTX 6] The Nakagawa declaration likewise teaches away from 2,3-dichloro substitution. The most potent compound reported in the Nakagawa declaration does not contain any chlorines. [Tr. 1642-43 (Nichols); Tr. 261-262 (Press); DTX 214] The

Nakagawa declaration also only lists mono- and unsubstituted compounds, teaching away from di-substituted compounds. [Tr. 1653 (Nichols); Tr. 259 (Press)]

Finally, Defendants point to *In re Zickendraht*, 319 F.2d 225 (C.C.P.A.), contending that "striking" similarities between that case and the present case compel a conclusion of double patenting here. *Zickendraht*, however, involved metalized diazo dyestuffs, not pharmaceuticals or potential antipsychotics. Defendants further mischaracterize the relevant claim differences at issue in *Zickendraht*. Those claim differences did not concern the presence or absence of chlorine substituents as Defendants contend, but instead concerned "the presence or absence of a methyl group on one of the benzene rings." *Zickendraht,* 319 F.2d at 1532. *Zickendraht* concerned a question of patentability in a pending patent application, which involves a lower standard of proof, and further concerned different facts from the present case. The Court concludes that *Zickendraht* does not support Defendants' double patenting argument.

For these reasons and all of the reasons discussed above in its obvious analysis, the Court holds that aripiprazole is not an obvious variant of the unsubstituted butoxy compound of claim 13 of the '416 patent.

Because the Court concludes that Defendants have not shown a *prima facie* case of obviousness, it need not consider the secondary considerations of nonobviousness discussed above in Section VI.A.5. The Court does conclude that this evidence is relevant, however, to the double patenting analysis presented here and further concludes that this evidence further supports the validity of the '528 patent claims.

C. Defendants' Unenforceability Defense

1. Legal Standards Relating to Unenforceability

a. Burden of Proof

Defendants have the burden to independently establish each element of inequitable conduct by clear and convincing evidence. *AstraZeneca Pharms. LP v. Teva Pharms. USA, Inc.*, 583 F.3d 766 (Fed. Cir. 2009).

In order to do so, Defendants must prove by clear and convincing evidence that, during the prosecution of the application for the '528 patent or during the reexamination of the '528 patent, each person that Defendants allege committed inequitable conduct (1) owed a duty of candor to the PTO, (2) withheld material information from the PTO or knowingly made a false statement to the PTO, and (3) acted with intent to deceive the PTO. *See, e.g., AstraZeneca*, 583 F.3d at 776; *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d at 1357 (Fed. Cir. 2008); *Exergen Corp. v. Wal-Mart Stores, Inc.,* 575 F.3d 1312 (Fed. Cir. 2009).

At least a threshold level of both materiality and intent to deceive must be proven by clear and convincing evidence. *Digital Control Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1313 (Fed. Cir. 2006).

Moreover, even if this threshold is met as to both materiality and intent, the Court must still balance the equities to determine whether the applicant's "conduct before the PTO was egregious enough to warrant holding the entire patent unenforceable. *Star Scientific*, 537 F.3d at 1365; *see also AstraZeneca*, 583 F.3d at 776-777.

The Federal Circuit has stressed that the high evidentiary burden associated with an inequitable conduct charge is designed "to mitigate the 'plague' whereby every patentee's imperfections [are]

promoted to 'inequitable conduct.'" *Allied Colloids, Inc. v. American Cyanamid Co.*, 64 F. 3d 1570, 1577 (Fed. Cir. 1995). The Federal Circuit recently reiterated that "[t]he need to strictly enforce the burden of proof and elevated standard of proof in the inequitable conduct context is paramount because the penalty for inequitable conduct is so severe . . . thus courts must be vigilant in not permitting the defense to be applied too lightly." *Star Scientific,* 537 F.3d at 1365-66.

b. Duty of Candor

Only certain individuals associated with the filing and prosecution of a patent application have a duty to conduct themselves with candor and good faith before the PTO. 37 C.F.R. § 1.56. Those individuals are:

> (1) Each inventor named in the patent application;
>
> (2) Each attorney or agent who prepares or prosecutes the application; and
>
> (3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with whom there is an obligation to assign the application.

37 C.F.R. § 1.56(a).

The duty of candor and good faith applies to individuals only and not to corporate entities or organizations. *Exergen*, 575 F.3d at 1329 (citing MPEP § 2001.01 (8th ed., rev. 2, May 2004)). Accordingly, Defendants may not simply allege that "Otsuka" or "the Finnegan firm" was aware of certain information allegedly withheld from the PTO. Defendants must identify specific individuals having a duty of candor.

Moreover, Defendants must prove that those specific individuals were aware of the allegedly material information. The duty of candor includes a duty to disclose to the PTO information

contemporaneously known to be material to the patentability of the pending claims. 37 C.F.R. § 1.56 There is no duty to disclose to the PTO information that was known years ago and is no longer known at the time of the proceedings before the PTO. *See* MPEP 2001.04 ("[T]he duty applies to contemporaneously or presently known information. The fact that information was known years ago does not mean that it was recognized that the information is material to the present application.").

There is no duty to disclose information that one is not actually aware of, nor is there any du1y to conduct a prior art search. *Nordberg, Inc. v. Telsmith, Inc.*, 82 F.3d 394 (Fed. Cir. 1996).

c. Materiality

For each item of information upon which Defendants rely to support their inequitable conduct defense, Defendants must prove by clear and convincing evidence that the item was material to the patentability of the subject matter claimed in the '528 patent. Material information is information for which there is "a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent." *Leviton Manufacturing Co., Inc. v. Universal Security Instruments, Inc.*, 606 F.3d 1353, 1358-59 (Fed. Cir. 2010) (citing *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1321 (Fed. Cir. 2000); and *Digital Control,* 437 F.3d at 1314).

Defendants also must show that each allegedly material piece of information is not cumulative to, or less relevant than, information that was considered by the PTO. An "'otherwise material reference is not material if it is merely cumulative to, or less relevant than, information already considered by the examiner.'" *Leviton,* 606 F.3d at 1358-59 (quoting *Larson Mfg. Co. v. Aluminart Prods Ltd.*, 559 F.3d 1317, 1327 (Fed. Cir. 2009); *see also AstraZeneca,* 583 F.3d at 773 (Fed. Cir. 2009).

d. Intent

To prove intent, Defendants must establish, by clear and convincing evidence, that the involved conduct, viewed in light of all the evidence, including evidence of good faith, must indicate sufficient culpability to require a finding of intent to deceive. *Golden Hour Data Systems, Inc. v. Emscharts, Inc.*, 2010 WL 3133539 at *8 (Fed. Cir. August 9, 2010) (citing *Digital Control*, 437 F.3d at 1319). Intent must be proven separately from materiality because "'materiality does not presume intent, which is a separate and essential component of inequitable conduct.'" *Star Scientific*, 537 F.3d at 1366 (quoting *GFI, Inc.v. Franklin Corp.*, 265 F.3d 1268, 1274 (Fed. Cir. 2001)).

Defendants alone bear the burden of proving deceptive intent. "'[A]n accused infringer cannot carry its threshold burden of showing intent to deceive simply by pointing to the absence of a credible good faith explanation.'" *Leviton,* 606 F.3d at 1363 (quoting *Larson*, 559 F.3d at 1341). Moreover, "[a]n inference of intent 'must not only be based on sufficient evidence and be reasonable in light of that evidence, but it must also be the single most reasonable inference able to be drawn from the evidence to meet the clear and convincing standard.'" *Golden Hour,* 2010 WL 3133539 at *8 (citing *Star Scientific*, 537 F.3d at 1366).

2. Defendants Have Not Established Any Inequitable Conduct

Defendants present four arguments in support of their unenforceability defense. Defendants argue allegedly inconsistent stereotypy data was withheld from the PTO, that the Nakagawa declaration was withheld from the PTO, that Otsuka's representatives presented false arguments during the reexamination of the '528 patent, and that Dr. Hirose falsely described the testing procedures underlying his declaration. Defendants have not carried their heavy burden of proof with respect to any of their allegations of inequitable conduct. Defendants have not established any material

withholding or misrepresentation of information from the PTO and further have not established any deceptive intent.

a. There Was No Withholding of Any Allegedly Inconsistent Stereotypy Data

Defendants' first argument in support of their unenforceability defense is that Otsuka withheld allegedly contradictory stereotypy test data concerning the 2,3-dichloro propoxy linked compound. This argument was not included in the inequitable conduct arguments listed in Defendants' Pretrial Order as required by this Court, and was not raised by Defendants until late in the trial, during the cross-examination of Dr. Oshiro. In entering the parties' Pretrial Order, this Court specifically ordered that no changes to the Pretrial Order would be permitted absent a showing of "manifest injustice." [D.I. 328 (Pretrial Order) at 70] Because Defendants have not made any such showing concerning this belated argument, the Court disregards this argument.

Even if the Court were to consider this argument, however, for the following reasons, Defendants have not proven there was any inequitable conduct relating to the allegedly withheld internal stereotypy data.

(1) The Internal Stereotypy Data Is Not Material

Defendants argue that internal Otsuka test data, showing that aripiprazole is allegedly six-times more potent than the 2,3-dichloro propoxy compound in the anti-apomorphine stereotypy test, is material to the patentability of the '528 patent claims because it is allegedly inconsistent with the data in the Hirose declaration, which shows that aripiprazole is twenty-three times more potent in this same comparison. Because Defendants did not raise this argument until late in the trial proceedings, the internal Otsuka test data and any alleged inconsistencies with the Hirose data were not addressed by

any of the parties' expert witnesses. For example, no evidence was presented concerning the test conditions underlying the internal Otsuka test data or whether these test data may be validly compared with the Hirose test data. Absent any such evidence, the Court declines to conduct its own analysis and comparison of the data.

The only testimony relating to these test data in any way was that of Dr. Oshiro, and Dr. Oshiro was never asked whether these data contradict the Hirose test results. Dr. Oshiro was never asked whether these data can be compared to the Hirose data. Defendants nevertheless contend that Dr. Oshiro testified that a six-fold difference in potency, such as shown in these internal test results, would not be unexpected. Dr. Oshiro's actual testimony, however, does not support any such conclusion. Defendants rely on Dr. Oshiro's testimony concerning test results for OPC-4392 and a compound created by replacing the propoxy linker group in OPC-4392 with a butoxy linker group. Dr. Oshiro testified that this structural modification to OPC-4392 did not result in the same "15-fold activity increase" he had seen when he had made a similar structural modification to his "seed compound," OPC 4310:

> A: As I indicated earlier, when the propoxy in 4310 was changed to butoxy, such as in 14542, the activity increased 15-fold. And so we wanted to confirm as to whether or not the OPC-4392 which was undergoing clinical testing would have the same activity increase, which is the 15-fold activity increase, if the propoxy was changed to butoxy. So we decided to synthesize the compound.
>
> Q: And what did you find?
>
> A: We did not find a considerable increase in the activity such as when we saw from 4310 to OPC-14542. In other words, even if the propoxy was changed to butoxy, we did not see a surprising increase, such as the 15-fold increase.

[Tr. 1772-73 (Oshiro)]

Defendants argue that Dr. Oshiro testified here that a six-fold difference in stereotypy test results is not surprising, because test data reported in later monthly reports showed six-fold difference in the stereotypy test results for OPC-4392 versus the butoxy-linked analog. Dr. Oshiro's testimony does not support that interpretation. Dr. Oshiro merely stated that the test data for OPC-4392 and its butoxy analog did not show the same fifteen-fold increase that he saw when he modified OPC 4310. As is apparent from Dr. Oshiro's actual testimony, Dr. Oshiro did not make any general statement about a six-fold increase in activity in the stereotypy test as Defendants contend. Dr. Oshiro was never asked to identify the stereotypy test data for OPC-4392 and its butoxy analog he had in mind when he offered this testimony, and it is unclear whether Dr. Oshiro recalled the specific details of those test results. To the extent Dr. Oshiro did recall specific test results for OPC-4392 and its butoxy analog, it is also unclear whether he was referring to the same test data cited by Defendants, because Defendants never asked.

Defendants never asked Dr. Oshiro his opinion concerning a six-fold increase in stereotypy test data and further never asked Dr. Oshiro if the internal Otsuka test data was inconsistent with the test data reported in the Hirose declaration. Defendants cannot now attempt to construct what answers Dr. Oshiro might have provided in response to these questions Defendants never posed. Defendants' strained and indirect interpretation of Dr. Oshiro's testimony cannot satisfy their burden of proving materiality by clear and convincing evidence.

(2) The Internal Stereotypy Data Were Not Withheld from the PTO With an Intent to Deceive

Defendants have not proven that any individual knowingly withheld this allegedly inconsistent data. Defendants allege that Dr. Oshiro was aware of the contents of the Hirose declaration and therefore must have intentionally withheld the allegedly contradictory internal data with an intent to deceive the PTO. Dr. Oshiro did not affirmatively testify, however, that he was aware of the test data submitted in the Hirose declaration. He merely testified that "most likely this draft – draft of this declaration was sent to me as an attachment to an e-mail requiring or requesting me to check the wording for the way things are worded in this document." [Tr. 1897 (Oshiro)] Dr. Oshiro's testimony, which reflects his uncertain memory in this regard, does not establish that Dr. Oshiro was aware of the specific details of the test data reported in the Hirose declaration. Because Defendants have not shown that Dr. Oshiro was aware of the specific data in the Hirose declaration, they cannot prove that he was aware of any contradiction.

Defendants also failed to offer any evidence concerning additional details underlying their allegation that Dr. Oshiro knowingly withheld contradictory test data. Defendants never inquired as to whether Dr. Oshiro recalled in 2005 the specific stereotypy test data Defendants cite. That data was generated in 1987, 18 years earlier, and was among dozens of test results reported in Dr. Oshiro's notebooks. [DTX 59T] It is therefore not apparent that in 2005 Dr. Oshiro would have recalled the details of the 1987 data and Defendants have not carried their burden of proof that he did. *See* MPEP 2001.04 (holding that the duty to disclose only applies to contemporaneously known information).

Defendants also never inquired as to whether Dr. Oshiro believed there was any contradiction between the Hirose data and the internal stereotypy data Defendants cite. On their face, data showing

a six-fold improvement and data showing a twenty-three-fold improvement are not contradictory, and Defendants have not presented any evidence that Dr. Oshiro believed to the contrary even had he been aware of these data.

Finally, Defendants suggest Dr. Hirose may have been aware of the allegedly contradictory test data because he generated test data for aripiprazole in 1987. This does not prove that Dr. Hirose was aware of the specific data Defendants cite, and Dr. Hirose testified that he did not recall whether he had seen any other comparative data concerning the compounds tested in the Hirose declaration. [Tr. 1968-1970 (Hirose)]

Accordingly, Defendants have not met their burden of proof by clear and convincing evidence that any individual knowingly withheld contradictory test data.

b. There Are No False Statements in the Hirose Declaration

Defendants' second argument in support of their unenforceability defense is that Dr. Hirose's declaration was allegedly false and misleading because Dr. Hirose did not follow the test procedures outlined in the protocol for the stereotypy testing attached as Exhibit 1 to his declaration. Again, Defendants have not proven that Dr. Hirose offered false statements with an intent to mislead.

(1) The Hirose Protocol Accurately Described the Testing Procedures

In this protocol, Dr. Hirose indicated that the "observation for stereotyped behavior will be performed by an observer blind to the treatment received by the mice." [PTX 20 at OPC0001665] Defendants contend that this statement indicates that only a single observer conducted all of the stereotypy testing and that this single observer would be blinded to the identity of the compound being tested, not just the doses of compound administered. Because two observers conducted the stereotypy

experiments and these observers were blinded to the doses administered but not the compounds, Defendants argue that Dr. Hirose did not follow his study protocol and suggest he did so with an intent to deceive.

The protocol, however, does not support Defendants' interpretation. The isolated statement cited by Defendants merely indicates that individual mouse observations would be performed by a single individual. It does not state that only one individual would be involved in the overall conduct of the study, as Defendants contend. [PTX 20] To the contrary, the Hirose protocol specifically identified two individuals, Dr. Hirose and Dr. Kikuchi, as the investigators who carried out the testing. Dr. Roth and Dr. Hirose each explained that it was therefore clear that two individuals would score the stereotypy testing. [Tr. 1100-01 (Roth); Tr. 1983-86 (Hirose); PTX 20 at OPC0001658] Defendants did not offer any testimony in response to Dr. Roth's or Dr. Hirose's testimony in this regard. Dr. Beninger, Defendants' only witness on this issue, did not refer in any way to the listing of two investigators in the protocol and, in fact, did not provide any clear testimony in support of Defendants' position that the Hirose protocol indicated that only a single individual would perform the stereotypy testing. [Tr. 958 (Beninger)] Accordingly, Defendants have not shown that the protocol indicates that the testing would be performed by a single individual.

Defendants likewise did not establish that the protocol indicated that the observers would be blinded to the identity of the compound being studied. The statement in the protocol refers to the "treatment received by the mice." [PTX 20 at OPC0001665] Because the observers were blinded to the dosage of compound administered to the mice, or whether the mice were instead administered the placebo, they were in fact blinded to the treatment received by the mice. As Dr. Roth explained, the statement in the protocol does not necessarily indicate that the observer was blinded to both the

identify of the compound and the dose of compound administered. [Tr. 1113-14 (Roth)] Moreover, as discussed above, Dr. Roth explained that the blinding methodology used by Dr. Hirose, where the observer was blinded to the dose administered to the mice, was sufficient to effectively blind the study. [*Id.*]

Dr. Hirose similarly explained that the mention of blinding in the protocol was referring to the fact that the observer was in fact blinded to the dose of test compound administered to the mice, which was in fact the treatment received by the mice. [Tr. 1930-31 (Hirose)] As Dr. Hirose further explained, this blinding methodology was the standard method employed at Otsuka, and Otsuka had used this same blinding methodology in experiments conducted for generating data for submission to the FDA and for publications in peer-reviewed journal articles. [Tr. 1931-33 (Hirose)] Moreover, as explained above in Section IV.J.5.b.(2), there is no merit to Defendants' speculation that the testing methodology used to generate the Hirose data rendered that data unreliable.

Accordingly, Defendants did not prove that the protocol did not accurately reflect the test methods used by Dr. Hirose in carrying out the stereotypy tests.

(2) Dr. Hirose Did Not Intend to Deceive the PTO

Defendants also have not shown that Dr. Hirose acted with deceptive intent in conducting the testing underlying his declaration. Dr. Hirose testified that he followed the procedures outlined in the study protocol on many prior occasions, and that these were the typical methods employed by Otsuka. [Tr. 1931-1933 (Hirose)] Dr. Hirose explained that these were the same methods used in generating data for submission to the FDA and for publication in peer-reviewed journal articles. [Tr. 1931-1932 (Hirose)] Dr. Hirose had no reason to believe that these test procedures would not also be satisfactory

to the PTO. Defendants have not established to the contrary, much less that Dr. Hirose acted with deceptive intent with respect to the conduct of the stereotypy testing.

Lacking any affirmative evidence, Defendants suggest that, because Dr. Hirose hoped that the data would be helpful for Otsuka, he must have intended to deceive the PTO. The evidence does not support that conclusion. Every declarant hopes that their declaration and any included data will be supportive of patentability. That does not mean that every declarant has deceptive intent, and Defendants cannot establish through this argument that Dr. Hirose acted with an intent to deceive the PTO.

Finally, Defendants contend that Dr. Hirose's testimony lacked credibility because he allegedly changed his testimony concerning the stereotypy scale, first stating that it is a subjective scale, and then stating that it is an objective scale. [Def. FOFCOL, page 154] This argument is absurd. At this point during Dr. Hirose's testimony there was clearly an error in the interpretation, as was explained on the record, and Dr. Hirose was therefore asked the same question a second time. [Tr. 1936] Defendants, who were using their own check translator, did not dispute that there was an interpretation problem or object to the question being posed again. Moreover, in correcting his mistranslated testimony, Dr. Hirose provided a detailed description of this position, demonstrating that his original answer had in fact been mistranslated.

Accordingly, Defendants have not shown that Dr. Hirose acted with an intent to deceive.

c. There Was No Inequitable Conduct with Respect to the Nakagawa Declaration

Defendants' third argument in support of their unenforceability defense is that the Nakagawa declaration was withheld from the PTO with deceptive intent. Again, Defendants have not proven that

this non-prior art document was material to the patentability of the '528 patent claims or that it was withheld from the PTO with an intent to deceive.

(1) The Nakagawa Declaration Is Not Material

Defendants contend that the Nakagawa declaration is material because the mouse jumping data disclosed therein allegedly indicate the superiority of a butoxy linker group over a propoxy linker group in an improved antipsychotic drug, thus suggesting that the test results reported in the Hirose declaration were not unexpected. [DTX 214; PTX 20] As discussed above, the Nakagawa test data do not support that conclusion.

The Nakagawa declaration does not include testing of any of the compounds tested in the Hirose declaration. Further, the mouse jumping data disclosed in the Nakagawa declaration are different from the stereotypy test data disclosed in the '528 patent and in the Hirose declaration. [Tr. 1244-46 (Roth)] Accordingly, the Nakagawa mouse jumping data cannot be directly compared with the data reported in the Hirose declaration.

As discussed above in Section V.C.1, Defendants also did not prove any relationship between the mouse jumping test data and the stereotypy test data and, in fact, there is no scientific correlation between results in one test with the other. [Tr. 1247-48 (Roth)] The evidence introduced at trial demonstrated that these two tests are not equivalent. Defendants contend that the unsubstituted butoxy compound displays excellent results in the mouse jumping test. This same compound is virtually inactive in the stereotypy test, indicating that the allegedly "excellent" mouse jumping data do not predict excellent results in the stereotypy test. [Tr. 1229-1232, 1239-1240 (Roth); PTX 564 at 661 (compound no. 4)] Moreover, while the stereotypy test has been widely used in antipsychotic drug

development, there is no evidence that the mouse jumping test has ever been used to develop a new antipsychotic drug. [Tr. 1243-44 (Roth); Tr. 253 (Press); Tr. 851-2 (Castagnoli)]

Even if there were a relationship between the mouse jumping data in the Nakagawa declaration and the stereotypy data presented in the Hirose declaration, the Nakagawa data do not show the general superiority of a butoxy linker over a propoxy linker as Defendants contend. Defendants focus on the mouse jumping data in the Nakagawa declaration relating to two compounds, the unsubstituted propoxy-linked compound and the unsubstituted butoxy compound. The mouse jumping test results concerning this pair of compounds do not establish the superiority of all butoxy-linked compounds, much less predict stereotypy test results for all butoxy-linked compounds. It was shown at trial that the butoxy-linked compound tested in the Nakagawa declaration, the unsubstituted butoxy compound, has very low potency in the stereotypy test, negating any argument that the Nakagawa data would suggest the superiority of this compound in the stereotypy test. [Tr. 1229-1232, 1239-1240 (Roth); PTX 564 at 661 (compound no. 4)]

The Nakagawa test data were also insufficient to support the conclusions that Defendants seek to draw from those data. The purpose of the data presented in the Nakagawa declaration was to show a difference in activity of the claimed compounds as compared to prior art compounds which were inactive in the mouse jumping test at the highest dose tested. [Tr. 1638-39 (Nichols); Tr. 255-256 (Press)] The data were not intended to show differences among the claimed compounds, including the unsubstituted propoxy and unsubstituted butoxy compounds, and the data were insufficient to establish any such differences. As Dr. Nichols explained, given the lack of detail concerning the precision of the reported data and the inherent variability in mouse data, one of ordinary skill in the art would not

draw any conclusions concerning the relatively small differences in potencies among the various claimed compounds reported in Nakagawa declaration. [Tr. 1638-45 (Nichols)]

Further, if anything, the data in the Nakagawa declaration teach away from the structural features of the claimed compounds tested in the Hirose declaration, including the use of a butoxy linker. The most potent compound presented in the Nakagawa declaration, test compound 44, has the linker group attached at the 5-position on the carbostyril core, not the 7-position, like the claimed compounds tested in the Hirose declaration. Compound 44 is also a propoxy-linked compound, not a butoxy-linked compound. [*Id.*] In fact, eight of the nine compounds tested in the Nakagawa declaration are propoxy-linked compounds. [Tr. 258 (Press); DTX 214] Therefore, if anything, the Nakagawa declaration teaches the superiority of, and a preference for, propoxy-linked compounds, not butoxy-linked compounds as alleged by Defendants.

The irrelevance of the Nakagawa mouse data is further established by the course of the reexamination proceedings relating to the '528 patent. During the reexamination proceedings, Otsuka submitted the Banno article, which included mouse jumping data for a number of compounds, including two of Defendants' proposed lead compounds (the unsubstituted butoxy compound and OPC-4392), and also the compounds included in the Nakagawa declaration. [Tr 537-552 (Goolkasian); DTX 214 at 4384 and 4386; DTX 84] The Examiner did not cite to any of these mouse jumping data in the reexamination proceedings, confirming that these data, which were distinct from the stereotypy data disclosed in the '528 patent and presented in the Hirose declaration, were not relevant to the patentability of the '528 patent claims. [PTX 121]

(2) The Nakagawa Declaration Was Not Withheld with Deceptive Intent

Defendants also did not prove that any individual withheld the Nakagawa declaration from the PTO with an intent to deceive. Defendants have only identified a single individual in their allegations of the alleged withholding of the Nakagawa declaration: Dr. Oshiro. Dr. Oshiro denied any knowledge of the Nakagawa declaration [Tr. 1861-62] and as discussed above in Section V.C.2, Defendants have not pointed to any credible evidence to the contrary.

Defendants further alleged that Otsuka's attorneys must have known of the Nakagawa declaration and that "[i]t is extremely unlikely that Mr. Van Horn . . . did not know of the Nakagawa declaration." Such unsubstantiated speculation cannot satisfy Defendants burden of proving deceptive intent by clear and convincing evidence. Nor can Defendants carry their burden by pointing to the fact that Mr. Van Horn did not testify at trial. Given that Defendants did not specifically accuse Mr. Van Horn of committing inequitable conduct and further did not identify any evidence in support of such an allegation, there was no reason for Mr. Van Horn to testify at trial. Moreover, there is no basis to draw any adverse inference from the fact that Mr. Van Horn did not appear to testify at trial. Otsuka informed Defendants that Mr. Van Horn would be available to testify at trial [Pretrial Order at 138], but Defendants did not seek to call him as a witness. Under these circumstances, courts will not draw an adverse inference. *See A.B. Dick v. Burroughs Corp.*, 798 F.2d 1392, 1400 n.9 (Fed. Cir. 1986) (holding that "[a]n unfavorable inference may not be drawn from the lack of testimony by one who is equally available to be called by either party").

d. There Were No False Statements During the Reexamination Proceedings

Defendants' final argument in support of their unenforceability defense is that Otsuka's representatives made allegedly false statements to the PTO during the reexamination proceedings. Again, Defendants have not proven that any individual knowingly presented false statements during the reexamination proceedings.

(1) The Identified Statements Were Not False

Defendants point to arguments Otsuka's representatives presented in a May 16, 2005 Amendment and a September 14, 2005 Request for Reconsideration. In these submissions, Otsuka's representatives responded to various claim rejections, including a claim rejection based on five exemplary compounds disclosed in the '416, '840 and DE '105 patents. Defendants quote Otsuka's representative's argument, presented in each of these submissions, that "there is no evidence that the five exemplary carbostyril derivatives identified by the Examiner have . . . the recited property of treating schizophrenia." Defendants contend that this argument is allegedly contradicted by mouse jumping data in the Nakagawa declaration, a document that was not before the PTO during the reexamination proceedings. [Def. FOFCOL, page 70]

Defendants' argument relies on a cropped quotation from these documents. The full argument concerning these five compounds disclosed in the '416, '840 and DE '105 patents, as set forth in the May 16, 2005 Amendment, actually reads as follows:

> Fourth, while these references may suggest that their compounds may be useful for treating central nervous disorders, generally, there is no evidence that the five exemplary carbostyril compounds identified by the Examiner have such properties, let alone the recited property of treating schizophrenia. In fact, all of the testing is directed to very different properties, such as antihistamine, anaesthesia, and analgetic

> activities. *See* Exhibit C ['416 patent] at Col 31, line 1 to col. 36, line 10.

[DTX 121 at 01274] This same argument is repeated in abbreviated fashion in the Request for Reconsideration, along with a citation to the full argument presented in the May 16, 2005 submission. [DTX 121 at 01348]

The full uncropped statement makes clear that Otsuka's representatives were referring to the documents that were the subject of the PTO's claim rejection, the '416, '840 and DE '105 patent, and the lack of experimental evidence in those documents concerning the treatment of schizophrenia. This statement is factually correct and Defendants have not introduced any evidence to the contrary. There was no dispute among the parties that the cited references did not contain any experimental evidence that any of the disclosed compounds had the property of treating schizophrenia. [Tr. at 129 (Press) ("there is no data in the '416 patent with respect to antipsychotic activity")] Thus, even accepting Defendants' interpretation of the Nakagawa test data, the full statement from the reexamination submissions is not in conflict with the Nakagawa declaration as Defendants suggest.

(2) There Is No Evidence that the Identified Statements Were Intended to Mislead

Defendants also have not offered any evidence that any individual was aware of the contradiction they allege in the identified statements or intended to mislead the PTO in offering these statements. Defendants focus on Dr. Oshiro, but there is no evidence that Dr. Oshiro reviewed these reexamination documents prior to their submission, was aware of these specific statements, or acted with any deceptive intent in this regard. Dr. Oshiro testified at trial that he did not remember providing any comments concerning the May 16, 2005 Amendment, and Defendants never inquired as to the September 14, 2005 Request for Reconsideration. [Tr. 1892 (Oshiro)]

Lacking any evidence concerning these documents, Defendants argue that Dr. Oshiro was "intimately involved with the reexamination proceeding." The record does not support any such conclusion. The evidence establishes that Dr. Oshiro did attend certain meetings concerning the reexamination proceedings and also exchanged certain written communications. As Dr. Oshiro explained, however, given his hearing disability, his attendance at meetings did not mean he was fully aware of the discussions that took place during those meetings. [Tr. 1874-1875 (Oshiro)] Moreover, Defendants did not established that Dr. Oshiro participated in the preparation of any specific documents submitted during the reexamination. [Tr. 1875 (Oshiro)] Defendants have not proven that Dr. Oshiro acted with deceptive intent.

3. Because There Is No Threshold Showing of Materiality or Intent, No Balancing is Necessary

Defendants have the burden of proving, by clear and convincing evidence, threshold levels of materiality and intent. Because Defendants have not done so with respect to any of their allegations of inequitable conduct, there is no need for the Court to conduct any balancing of materiality versus intent in an overall determination of inequitable conduct. Defendants have not proven any of their allegations of inequitable conduct.

VII. REMEDIES

In accordance with 35 U.S.C. § 271 (e)(4)(A), Otsuka is entitled to an order that the effective date of any approval of Defendants' respective ANDAs be a date which is not earlier than the expiration date of the '528 patent (currently set to expire on April 20, 2015, including a six-month period of pediatric exclusivity). In particular, 35 U.S.C. § 271 (e)(4)(A) states that, when the filing of an ANDA is found to be an infringing act, "the court *shall* order the effective date of any approval

of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." (Emphasis added). *See also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 2007 U.S. Dist. LEXIS 19494, at *3-6 (D.N.J. 2007), *aff'd*, 520 F.3d 1358 (Fed. Cir. 2008) (where, subsequent to a finding of infringement, the Court ordered that the effective date of defendant's ANDA be reset to a date not earlier than the expiration date of the patent at issue, even where the effective data had already been set by the FDA prior to the finding of infringement).

In addition, in accordance with 35 U.S.C. § 271 (e)(4)(B), Otsuka is entitled to a permanent injunction against Defendants and their officers, agents, attorneys, and employees and those acting in privity or concert with them, enjoining them from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of Defendants' generic aripiprazole products described in Defendants' respective ANDAs during the remaining term of the '528 patent. As set out in the U.S. Supreme Court's decision in *eBay Inc. v. MercExchange, L.L.C.,* 547 U.S. 388 (2006), in determining whether to grant a permanent injunction, a court must weigh the following four factors: (1) whether plaintiff would suffer an irreparable injury; (2) whether remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) whether, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) whether the public interest would not be disserved by a permanent injunction. *Id.* at 391.

In accordance with the trial management conference held before the Court on July 23, 2010, once the Court is in a position to enter final judgment on the merits, the entry of a permanent injunction does not require a finding of irreparable harm. *See* Draft Transcript of Motion Hearing, July

23, 2010, at pages 13-15 ("THE COURT: A permanent injunction is entered when the Court is in a position to enter final judgment, and a permanent injunction does not require any finding on the issue of irreparable harm. It is a final ruling on the merits. There is no irreparable harm analysis in imposing a final injunction.") With respect to the second *eBay* factor, remedies available at law, such as money damages, would be inadequate to compensate for the irreparable injury that Otsuka would suffer upon a denial of a permanent injunction. With respect to the third *eBay* factor, the balance of hardships also weight in favor of Otsuka. In particular, added erosion of markets, customers, and prices is rarely reversible. Moreover, without the permanent injunction, plaintiff Otsuka would lose the value of its '528 patent, while Defendants would only lose the ability to go onto the market and begin earning profits earlier. Finally, with respect to the fourth *eBay* factor, the public's interest in encouraging investment in innovation by upholding valid patents outweighs the public's interest in lower cost drugs, particularly where, as here, a patent has already been found to be valid, enforceable, and infringed. As such, the *eBay* factors each weigh in favor of Otsuka, and Otsuka is thus entitled to a permanent injunction against Defendants in this case.

Respectfully submitted,

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_____/s/_____

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CERTIFICATE OF SERVICE

It is hereby certified that a true and correct copy of the foregoing (1) PLAINTIFF'S POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW and (2) Certificate of Service was served by the undersigned this October 12, 2010, via electronic mail with a confirmation copy by Federal Express to:

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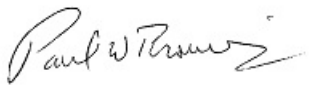

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